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AMAAC Introduction
The Arab Medical Association Against Cancer (AMAAC) is a medical body that was established in 2001 as part of the Arab Medical Association where its main office is located in Cairo - Egypt, and it is also a continuation of the Arab Council Against Cancer that was founded in 1995. The Executive Committee of (AMAAC) is represented by two members who are named officially by the Oncology Society of each Arab Country.

The Arab Medical Association Against Cancer aims at strengthening relationships between members in different Arab Countries to raise the level of cooperation in the field of oncology on both scientific and practical aspects. Exchanging information and researches between members through Regional and Arab Conferences and Publications. Holding Public Awareness Campaigns in the field of oncology that are organized by Arab Countries. Participating in scientific activities with International Oncology Societies. Finally, encouraging researchers and doctors to meet and exchange experiences together with finding training opportunities in the field of oncology inside and outside the Arab World.

The Executive Board of AMAAC

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Addition of Bevacizumab or Cetuximab to First Line Chemotherapy in the Treatment of K-ras Wild type metastatic Colorectal Carcinoma

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Key words: Metastatic colorectal cancer (mCRC), K-ras wild type, Bevacizumab, Cetuximab, Egypt.
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Abstract

Purpose: Mutations in K-ras gene are found in 30–40% of colorectal carcinoma (CRC) and are associated with poor response to Cetuximab or Panitumumab. Thus, K-ras testing is mandatory for patients with metastatic CRC (mCRC) but genotyping mistakes can be a result of many factors. The combination of Capecitabine with Irinotecan (XELIRI) was proven effective and addition of Bevacizumab as well as Cetuximab was studied with good tolerance and promising results. The aim of this study was to compare the efficacy and safety of XELIRI-Bevacizumab with that of XELIRI-Cetuximab in the first-line treatment of K-ras wild type mCRC.

Patients and methods: This is pilot study including 20 patients with mCRC K-ras wild type treated at Saudi German hospital, KSA & private center in Cairo, Egypt. The primary objective was to confirm non-inferiority of XELIRI-Bevacizumab compared with XELIRI-Cetuximab for progression-free survival (PFS).

Results: At median follow up of 12 months, the overall response rate (ORR) was 45% with 1-year PFS 75%. Comparing the 2 arms, ORR was 50% in Arm 1 compared to 40% in Arm 2 (p=0.952) while clinical benefit was 60% in both arms. PFS at 1-year was 80% in Arm 1 versus 70% in Arm 2 (p=0.612) with HR 0.63 (95%CI 0.10 - 3.79).

Conclusion: Adding Bevacizumab to XELRI is not inferior to adding Cetuximab to the same regimen in 1st line therapy of K-ras wild mCRC with acceptable and manageable toxicity profiles and maybe preferable in absence of accurate and reliable K-ras testing.

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide in both males and females, and is the second leading cause of cancer related mortality in western countries.1 In Egypt, it is the 7th common malignancy with an annual incidence of 3.3%. 2 Despite improvements in the screening programs, 20% of patients present with metastatic tumors.1

K-ras, an essential component of the EGFR signaling cascade, can acquire mutations in exon 2, isolating the pathway from the effect of EGFR thus rendering EGFR inhibitors ineffective. Mutations in the K-ras gene are found in 30%–40% of colorectal tumors 2 and are associated with a poor response to Cetuximab or Panitumumab.3 Independent reanalysis of eight randomized clinical trials showed inadequate response for these drugs when a K-ras codon 12 or codon 13 mutation was present 1. As a result, K-ras testing is now mandatory at the presentation of metastatic disease in patients with CRC.6-7 K-ras mutation in CRC were found to have relations to the patients’ age and sex; with the K-ras mutations being much less frequent in male than female patients at younger ages (≤ 40 years, odds ratio < 0.014). The low frequency might indicate that a different, ras-independent, pathway to neoplasia is dominating in the colon of younger males.8 For decades, treatment of mCRC was limited to 5-fluorouracil (5FU) / Leucovorin (LV), with a median OS of about 12 months.9 Oral fluoropyrimidines (Capecitabine, Uracil) showed better response rates (RR) and better tolerability, as compared to the infusional 5FU, with comparable OS benefits.10-11 Two other chemotherapy agents, i.e. Irinotecan and Oxaliplatin, have shown activity in the treatment of mCRC when combined to fluoropyrimidine backbone, providing a variety of regimens (FOLFOX, FOLFIRI, IFL, XELOX, XELIRI...), with improvements in RR, progression free survival (PFS) and OS as compared to 5FL/LV only.12-15 Recently, the introduction of targeted therapies in the treatment of mCRC has greatly improved the outcomes. Two types of monoclonal antibodies were approved for the clinical use in mCRC; the anti vascular endothelial growth factor (VEGF) receptor antibody, bevacizumab and the anti epidermal growth factor receptor (EGFR) antibodies: Cetuximab and Panitumumab.16-18 The combination of Capecitabine with Irinotecan (CAPIRI) was proven effective and safe in a large randomized trial.19 Addition of Bevacizumab to XELIRI was shown to be not inferior to FOLFIRI-Bev in randomized studies.20-22 Also, Cetuximab was studied in addition to XELIRI with good tolerance and promising results.23 The aim of this study was to compare the efficacy and safety of XELIRI-Bevacizumab with that of XELIRI-Cetuximab in the first-line treatment of K-ras wild type metastatic colorectal carcinoma (mCRC).
Patients and methods

This pilot study included 20 patients with metastatic K-ras wild type colorectal carcinoma treated at Saudi German hospital, KSA & a private center in Cairo, Egypt. The primary study objective was to confirm non-inferiority of XELIRI-Bevacizumab compared with XELIRI-Cetuximab for progression-free survival (PFS) in patients with K-ras wild type mCRC.

Inclusion criteria:
1. Pathologically proven adenocarcinoma of colorectal origin
2. Metastases radiologically documented that couldn’t be resected with curative intent
3. No detected mutations in codon 12 and 13 of K-ras gene by real time PCR on primary resection block or metastatic disease if feasible.
4. At least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria
5. Previous adjuvant chemotherapy (FOLFOX) more than 6 months prior to enrollment.
7. Age: 18 years or more.
8. Gender: both male and female.
9. Good cardiac, renal & hepatic functions.
10. Written informed consent.

Exclusion criteria:
1. Evidence of any CNS metastases.
2. Bleeding tendency.
3. Severe co-morbid disease including uncontrolled hypertension.
4. Patients with second malignancy.
5. History of anti-cancer agents in the last 6 months.

All patients underwent complete history taking, physical examination, laboratory investigations including: complete blood count, serum creatinine, prothrombin time & concentration, ALT, AST, serum albumin, total & direct bilirubin. Imaging investigations included: C.T scanning of chest, abdomen & pelvis for assessment of metastatic disease.

All patients were treated for 1st line metastatic disease with systemic chemotherapy XELIRI (Capecitabine PO 1700 mg/m²/d in 2 divided doses at days 1-14 plus Irinotecan 200 mg/m² over 90 minutes i.v infusion on day 1 only) every 3 weeks plus either Bevacizumab 7.5 mg/Kg every 3 weeks (Arm 1) or Cetuximab weekly (initially 400 mg/m² I.V. [120 minutes], subsequently 250 mg/m² [30 minutes]) (Arm 2). Routine antiemetic prophylaxis with a 5-hydroxytryptamine-3-receptor antagonist was used in both arms. Treatment was administered until disease progression, unacceptable toxicity or consent withdrawal.

Patients were assessed for toxicity before each cycle using the National Cancer Institute Common Toxicity Criteria version 3.0. Chemotherapy was delayed until recovery if neutrophils were less than 1.5×10⁹/L or platelets less than 100×10⁹/L, or for significant (more than grade-II) persisting non-hematologic toxicity.

Response to treatment was evaluated using CT scan with contrast every 9 weeks according to the RECIST criteria.

Statistical analysis

The primary endpoint of the study was PFS. Secondary endpoints were clinical benefit and safety profile.

PFS was defined as the interval from the time of enrolment to the date of first documented disease progression or patient’s death from any cause. Clinical benefit was defined as partial or complete response in addition to stable disease. The primary analysis of PFS was of the non-inferiority of Arm 1 to Arm 2, as measured by the hazard ratio HR_Arm1 vs Arm2 with a non-inferiority margin of 1.40; H0 was rejected if the upper limit of the 95% confidence interval (CI) was less than the non-inferiority margin. The Kaplan–Meier method was used to estimate PFS curves, and log-rank test was used to compare curves. Cox proportional hazards modeling was used to calculate hazard ratio (HR) and confidence intervals (CIs). \(^2\)-tests were used to compare toxicity and response rates. \(P\)-values less than 0.05 were considered statistically significant for all comparisons. SPSS program (version 17.0) was used for all analyses.

Results

From June 2009 to December 2010, twenty patients with unresectable mCRC were enrolled into the study. The median age for the studied patients was 56.5 years (range 43 - 69) with 65% of them had PS 0-1 at presentation. Liver was the most common site of metastasis in both arms (80% in Bevacizumab arm versus 100% in Cetuximab arm). Both arms were well balanced with no difference regarding age, PS as well as sites of metastasis. Detailed clinicopathological characteristics are shown in table (1).

At a median follow up of 12 months, the overall response rate (ORR) was 45%. Comparing the 2 arms, the ORR was 50% in Arm 1 compared to 40% in Arm 2 (\(p=0.952\)) while clinical benefit was 60% in both arms [table 2].

Regarding survival, 1-year PFS for the whole group was 75%. Comparing both arms, 1-year PFS was 80% in Arm 1 versus 70% in Arm 2 (\(p=0.612\)) with HR 0.63 (95%CI 0.10 - 3.79) [Figure 1].

Concerning toxicity, both regimens were well tolerated; diarrhea was the most encountered adverse event in both arms (50% in Cetuximab arm & 20% in Bevacizumab arm) while hand & foot skin reaction was encountered in 10% of patients in each arm. [Table 3]

Discussion

Median survival of patients with metastatic CRC has been considerable improved with FOLFIRI or FOLFOX regimens. Addition of monoclonal antibodies targeting either VEGF or EGFR to Irinotecan combination chemotherapy in mCRC has demonstrated an increase in RR, PFS and mOS compared with chemotherapy alone.

Moreover, the use of the oral fluoropyrimidine Capecitabine with Irinotecan (XELIRI) in combination with Bevacizumab or Cetuximab has been reported to be safe and effective in the first-line treatment for metastatic CRC. To the best of our knowledge, the current study is the first randomized trial comparing Bevacizumab versus Cetuximab in combination with the outpatient XELIRI regimen. The primary endpoint was met as no statistically significant difference has been observed between the two treatment arms.

The efficacy parameters of XELIRI-Bevacizumab are in same range with that reported in previous trials. ORR was 50% with 1 year PFS 80% in our study trial compared to 40% and 43% in Souglakos et al; same as regard XELIRI-Bevacizumab.
Cetuximab regimen, ORR was 40% with 1-year PFS 70% similar to Uygun et al. who reported ORR of 41.2% and 1-year PFS 55.4%. Earlier trials evaluating chemotherapy regimen with Capecitabine and Irinotecan had showed that XELIRI regimen was associated with unacceptable incidences of severe gastrointestinal adverse effects with grade 3-4 diarrhea up to 36% of patients. These effects were not seen in recent studies that used lower doses of both Capecitabine and Irinotecan without compromising efficacy which we used in our study.

Drugs targeting EGFR had improved survival in metastatic colorectal cancer. However, these therapies are effective only in patients harboring a tumor with a wild-type KRAS gene. Thus, the appropriate selection of patients with colorectal cancer for treatment with anti-EGFR drugs is a major challenge. Genotyping mistakes can be a result of many factors. A very important factor is the starting material as the type of fixative used has an impact on the quality of the assay. Some fixatives such as non buffered formalin do not allow molecular testing as it leads to low DNA quality. This might be the cause of false results. Another important issue in K-ras genotyping is the method used for testing. Two basic methods are predominantly used for KRAS testing: DNA sequencing and allele-specific PCR. Sequencing is usually used to detect point mutations but its major disadvantage is that it is less sensitive, and with samples with low tumor content, analysis might be difficult. Allele-specific PCR is more sensitive but tests for only a subset of the most common mutations, whereas sequencing can detect all possible mutations. Thus, in the absence of a national external quality assessment scheme, accurate and reliable K-ras testing is questionable and hence drugs depending on that test should be used with caution.

The major limitations of our study were the small number of patients included as well as the short follow up time, which might have influenced our findings and resulting in broad confidence intervals.

Although our results should be confirmed by prospective, randomized, phase-III trial, we think that they contribute to the literature because efficacy of Bevacizumab in comparison to anti-EGFR Cetuximab or Panitumumab in K-ras wild type mCRC was never studied until the recent presentation of results of FIRE-3 study in ASCO 2013 which was presented as Late breaking abstract showing better response rate of FOLFIRI-Cetuximab compared to FOLFIRI-Bevacizumab (72.2% vs 63.1%) but with no difference in PFS.

In conclusion, adding Bevacizumab to outpatient regimen XELIRI is not inferior to adding Cetuximab to the same regimen in the 1st line therapy of K-ras wild type mCRC with acceptable and manageable toxicity profiles and maybe preferable in absence of accurate and reliable K-ras testing.

Conflict of Interest: All authors declared no conflict of interest.

Tables

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References


Figures

Fig 1: Progression Free Survival according to treatment arm.
or capecitabine/oxaliplatin in combination with bevacizumab is effective and safe as first-line therapy for metastatic colorectal cancer: a randomized phase II study of the AIO colorectal study group. Ann Oncol 24: 1580-1587, 2013.


Correlation between Hepatocellular Carcinoma and Hepatitis C genotypes and their role in Hepatocarcinogenesis

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Key words: Hepatocellular carcinoma, Hepatitis C Virus, Genotypes, hepatocarcinogenesis.

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Abstract

Background: Hepatitis C virus (HCV) is known to be a major risk factor for the development of hepatocellular carcinoma (HCC).

Aim of the work: to correlate HCV genotypes among HCV positive cases of HCC with the clinicopathological profiles of patients, and to assess if there is a characteristic pattern of the virus that may accelerate oncogenesis.

Patients and methods: A prospective study; 60 patients; two groups: Group I: 30 patients: HCV with superadded HCC; Group II: 30 patients: HCV without superadded HCC (control); recruited from Alexandria University hospitals, Egypt. Confirmation of HCV infection and virus RNA extraction were done. The extracted HCV RNA was transformed to complementary DNA (cDNA) using reverse transcription PCR. INNO-LiPA HCV II was used to identify the genotype spectrum of the 60 samples.

Results: Most of HCC patients were in the 6th decade, males, of rural residence, fibrosis and cirrhosis and ultimately may lead to the development of HCC. However, the incidence in the United States has increased during the past two decades, possibly due to a large pool of people with longstanding chronic hepatitis C. (5,6)

Males are far more likely to develop HCC than females. The disparity is more pronounced in high incidence regions, where males are affected 2.1 to 5.7 times more frequently than females. (7)

The majority of HCCs occur in patients with chronic liver disease or cirrhosis; at a mean age at presentation between 50 and 60 years. (8,9) In sub-Saharan Africa, however, the mean age of presentation of HCC is decreasing, with a mean age of 33 years. (10)

Hepatitis C virus (HCV) causes more than 90% of parenterally transmitted non-A, non-B hepatitis (NANBH). (11) In more than 85% of HCV infections, chronic hepatitis is established and may slowly progress to worsening stages of fibrosis and cirrhosis and ultimately may lead to the development of HCC. (12,13)

In Egypt, approximately 13.8% of the population is infected, and 10% with chronic HCV. (14) The prevalent genotype in Egypt is type 4, with the presence of other genotypes. (15) In Europe and USA, HCV-1a and -1b, HCV-2a and -2b, and HCV-3a are the most common subtypes. Types 5 and 6 have been identified in South Africa and Hong Kong, respectively. (16)

Hepatitis C virus has a high rate of mutation during replication, and it exists in the bloodstream of infected persons as complex distributions of mutants known as viral quasispecies, which fluctuate during the course of the disease, mainly as a result of immune response. (17,18)

Clinical and epidemiologic studies suggest that HCV is more hepatocarcinogenic than HBV, as the frequency of HCC development among HCV-induced cirrhosis is much higher than that of HBV-induced cirrhosis. (19)

Unlike HBV, HCV is an RNA virus that does not integrate into the host genome. Instead, host-viral protein interactions seem to be the major pathways of hepatocarcinogenesis. The proteins widely reported to be associated with HCV-mediated hepatocarcinogenesis are core, NS3 and NS5A proteins, which have all been shown to inhibit p21WAF1 tumor suppressor expression post-transcriptionally. (20,21)

Hepatocellular carcinoma (HCC) is one of the most common types of malignant tumors that carry a poor prognosis worldwide. In Egypt, it is the second most common malignancy in males and the fifth in females. (1,2)

The incidence of HCC varies widely according to geographic location. High incidence regions (more than 15 cases per 100,000 population per year) include sub-Saharan Africa, the People’s Republic of China, Hong Kong, and Taiwan. (3) Over 40 percent of all cases of HCC occur in China, which has an annual incidence of 137,000 cases (4). North and South America, most of Europe, Australia and parts of the Middle East are low incidence areas with fewer than three cases reported per 100,000 population per year. However, the incidence in the United States has increased during the past two decades, possibly due to a large pool of people with longstanding chronic hepatitis C. (5,6)

Males are far more likely to develop HCC than females. The disparity is more pronounced in high incidence regions, where males are affected 2.1 to 5.7 times more frequently than females. (7)

The majority of HCCs occur in patients with chronic liver disease or cirrhosis; at a mean age at presentation between 50 and 60 years. (8,9) In sub-Saharan Africa, however, the mean age of presentation of HCC is decreasing, with a mean age of 33 years. (10)

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Aim of the work

In Patients having HCV infection, with and without superadded HCC, we aimed at identifying HCV Genotypes Spectrum, investigate their role in hepatocarcinogenesis and to correlate HCV Genotypes and viral loads to clinical and biochemical profiles of the patients.

Patients and Methods

A prospective study including 60 patients in two groups: **Group I**: 30 patients with HCV with superadded HCC. **Group II**: 30 patients with HCV without superadded HCC (control group). Approval by Ethics Committee of Faculty of Medicine, Alexandria University was obtained.

Patients were recruited from Clinical Oncology, Hepatology and Internal Medicine departments, Alexandria University hospitals, Faculty of Medicine, University of Alexandria. Eligibility Criteria included patients 20-70 years old; any stage of HCC; and signed informed consent.

All Patients were subjected to: History taking and complete physical examination, abdominal ultrasonography, triphasic CT of the liver (done to all patients in Group I and 3 patients from Group II), laboratory and biochemical investigations: serology for HCV infection using anti-HCV IgG 3rd generation ELISA kit, complete blood picture (CBC), liver transaminases (ALT, AST and GGT), serum bilirubin and Serum albumin.

HCC (for patients in Group I) was diagnosed according to EASL criteria, all had radiological evidence of HCC in either CT or US or both, and alpha fetoprotein (AFP) level above 400 μg/l. Seven patients had liver biopsy to confirm diagnosis. Barcelona Clinic Liver Cancer (BCLC) Group system was used for staging.

Patients in both groups were subjected to HCV Viral RNA extraction using Qiagen Kit. Viral loads were determined by real time PCR. HCV genotyping was tried using Multiplex-PCR with the specific primers for different HCV genotypes; however it did not work, so we worked using INNO-LiPA II kit. Results were interpreted using INNO-LiPA charts.

Randomly selected eight samples (4 from each group) were subjected to cloning and sequencing of PCR-amplified fragments of 5’ Untranslated Region (5’UTR) through the following steps:

a. Expected PCR-amplified fragments were excised from the agarose gel and purified using Qiagen Gel Extraction kit (Qiagen, Germany).

b. Cloning and subcloning into an eukaryotic vector as a step towards sequencing was done using TOPO TA Cloning® Kit for Sequencing.

c. Plasmid DNA was isolated using QIA Spin miniprep kit (Qiagen, Germany). Plasmid DNA was sequenced in both directions using BigDye Sequencing Kit and ABI 377 DNA sequencer (ABI, USA).

To compare the resulted 5’UTR sequences, pairwise and multiple DNA sequence alignment were carried out using CLUSTALW (1.82). Bootstrap neighbor-joining tree (Saitou and Nei, 1987) was generated using MEGA 2.1 (Kumar et al., 2001) from CLUSTALW alignments.

Results

Demographic data were comparable in both groups regarding age, sex and residence. Mean age was 56.2 years in group I and 57.3 years in group II. Only few patients in both groups were below 30 years (10% and 6.7% respectively). Sex distribution showed obvious male predominance. Group I included 80% males while group II included 83.3%. Majority of patients were from rural areas (63.3% in Group I and 56.7 % in group II). (Table 1).

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>30 – &lt; 40</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>40 – 50</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>60 or more</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Range</td>
<td>28 – 67</td>
<td>27 – 68</td>
</tr>
<tr>
<td>Mean</td>
<td>56.2</td>
<td>57.3</td>
</tr>
<tr>
<td>S.D.*</td>
<td>13.65</td>
<td>11.85</td>
</tr>
<tr>
<td>T - value</td>
<td>0.85</td>
<td>0.34</td>
</tr>
<tr>
<td>p - value</td>
<td>0.34</td>
<td>0.85</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Sex X2</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>p</td>
<td>0.738</td>
<td>0.738</td>
</tr>
</tbody>
</table>

Table 1: Demographic data.

<table>
<thead>
<tr>
<th>Residence</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Urban</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Residence X2</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>p</td>
<td>0.738</td>
<td>0.738</td>
</tr>
</tbody>
</table>

*Standard deviation

History of blood transfusion was comparably present in both groups (36.7% in group I and 30% in group II). On the other hand, history of schistosomiasis and clinical jaundice (>2 mg/dl) were only represented in group I (33.3% and 20 % respectively).

At time of sampling, serum AFP level was significantly higher in group I as a level of 400 μg/l or above was an inclusion criterion for this group. The mean in group I was 520.6 μg/l versus 8.69 μg/l in group II. AST, ALT, GGT and bilirubin levels were also significantly higher in group I; while serum albumin was significantly lower. (Table 2).

All patients in group I (30 cases) had high GGT, 84% had high ALT, and 56% had high AST levels.

<table>
<thead>
<tr>
<th>Group</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP (μg/l)</td>
<td>Mean</td>
<td>520.6</td>
</tr>
<tr>
<td>p</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>Mean</td>
<td>165.6</td>
</tr>
<tr>
<td>p</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>Mean</td>
<td>175.65</td>
</tr>
<tr>
<td>p</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>Mean</td>
<td>130.0</td>
</tr>
<tr>
<td>p</td>
<td>0.60</td>
<td></td>
</tr>
</tbody>
</table>
Table 3 shows Triphasic CT findings in group I where 60% of patients with HCC presented with 2 lesions. The mean size of lesions was 5.6 cm. Intra-abdominal lymph nodes were evident in around 13% of patients. Half of the patients had cirrhosis; almost third of them had hepatic fibrosis; while 16.7% had mixed cirrhosis and fibrosis.

Table 3: Triphasic CT findings in group I patients.

<table>
<thead>
<tr>
<th>No. of lesions</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23.3</td>
</tr>
<tr>
<td>2</td>
<td>60.0</td>
</tr>
<tr>
<td>3</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Table 4: Child Pugh classification and BCLC staging for group I patients.

<table>
<thead>
<tr>
<th>Child classification</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child A</td>
<td>25.6</td>
</tr>
<tr>
<td>Child B</td>
<td>54.9</td>
</tr>
<tr>
<td>Child C</td>
<td>19.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BCLC staging</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A</td>
<td>10.0</td>
</tr>
<tr>
<td>Stage B</td>
<td>56.6</td>
</tr>
<tr>
<td>Stage C</td>
<td>26.7</td>
</tr>
<tr>
<td>Stage D</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Most of HCC patients were grouped under B in Child Pugh classification (54.9%); most of them were staged as BCLC stage B (56.6%). (Table 4)

HCV viral loads were found to be significantly higher in HCC group, with a mean of 4.23 x 10^5 compared to a mean of 8.78 x 10^4 in the control group; taking into account that all patients did not receive systemic antiviral treatment. Moreover, viral loads quantity tended to be higher in more advanced stages of HCC. (Table 5)

Genotyping of HCV was attempted for all 60 patients using INNO-LiPa HCV II and results were interpreted using INNO-LiPa HCV II interpretation chart. All samples showed genotype 4 with no subgenotypes detected. (Figure 1).

Fig 1: HCV Genotyping by INNO-LiPa HCV II showing Genotype 4 in all samples

Comparison between the 4 isolates of each group was done. Samples showing similarity less than 97% were considered as subgenotypes. Isolate HCV4 from group I as well as isolate HCV6 from group II showed similarity.
with the other three isolates ranging from 87% to 96%. This means that each sample was considerably different from the other three; perhaps denoting a new subgenotype.

Multiple sequence alignment of the 4 samples from each group was done. For group I, minor differences between samples 1, 2 and 3 were noted, while the three samples were different considerably from sample 4. Similarly, minor differences between samples 5, 7 and 8 of group II were noticed, while they were different considerably from sample 6.

Phylogenetic analysis of the 4 DNA sequences of HCV 5'UTR from group I using Mega 4 program showed that the four examined 5 UTR regions were divided into two main groups having one ancestor. Group one contained samples HCV1, 2 and 3, while group 2 contained only sample HCV4. The same was observed in group II samples; group one contained samples HCV5, 8 AND 7, while group 2 contained only sample HCV6. This means that sample 4 and 6 are different considerably from the other 3 samples in each group.

To confirm the results, comparison of the 8 samples together showed that isolates 4 and 6 were different from the other 6 isolates, while showing high similarity to each other. Alignment of the 8 samples together shows that isolates 4 and 6 are different from the other 6 isolates, and show high similarity to each other.

The examined 5'UTR of the different 8 patients' samples were grouped into two main groups. Group one consisted of 6 sequences (HCV 1, 2, 3, 5, 7 and 8), while, the second group consisted of only two sequences (HCV 4 and 6). Group one was further divided into two main subgroups, subgroup one contains (HCV2, 8, 5, 7 and 1) and subgroup 2 included only one UTR (HCV3). This denotes that the two samples 4 and 6 may represent subgenotypes from genotype 4.

In conclusion; no significant pattern was characteristic to one group over the other; the 5'UTR from both groups were similar and there were no evident mutations present in group I characterizing the virus. Two sequences (sample 4 from group I and sample 6 from group II) showed similarity less than 97% with the other 6 sequences, while they show high similarity to each other and gathered in one ancestor in phylogenetic analysis. These two sequences can be considered a subgenotype from Genotype 4 that is present in Egyptian patients. However, larger trials are needed to confirm these results.

Discussion

The mean age of patients in group I with HCC was 57 years, which is similar to the age incidence in Western Europe and Asia (50-60 years), while in sub saharan Africa the mean age of incidence is 33 years.

The majority of cases in both groups of our study were males (80%), from rural origin (60%). This high incidence of HCV and HCC in males from rural areas may be attributed to schistosomiasis treatment given by I.V. injection. In one rural area of Egypt when the use of disposable syringes was unknown.

Bruno et al. (26) found that old age and male sex are independent risk factors for the development of HCC in anti-HCV positive cirrhotic patients. Tsai et al.(27) found that male cirrhotic patients developed HCC more frequently than did female cirrhotic patients, but the difference was not significant, and the frequency of HCC development was higher in those older than 50 years. Their results agree with ours.

History of blood transfusion was present in 36% of patients in group I and 27% in group II. This showed that blood transfusion may be a leading cause of transmission of HCV especially in the era before efficient routine laboratory screening of blood.

Comparable to our results, Kiyosawa et al. showed that 94.4% of patients with HCC in their series (54 cases) were positive for anti-HCV and in 42% of patients (21 cases) history of blood transfusion was documented. (28) On the other hand, Darwish et al.(29) found no association between blood transfusion and HCV seroprevalence.

Thirty two percent of patients in group I had past history of schistosomiasis with anti-schistosomal parental therapy. This agrees with results by Darwish et al.(29) which showed that schistosomiasis was significantly associated with HCV infection. Moreover, Abdel Wahab et al. found that 54.1% of patients with HCV were positive for anti-HCV; of them 32.9% had schistosomal infection. (30)

In the present study, laboratory investigations were used to assess the progression of liver disease. There was significant difference between the two groups regarding liver transaminases (ALT and AST), Gamma-glutamyl transferase (GGT), and alpha fetoprotein (AFP) levels. All patients in group I (30 cases) had high GGT, 84 % had high ALT, and 56 % had high AST levels. This showed that GGT may be the most sensitive test for assessment of deterioration in liver status and perhaps the development of HCC in patients with HCV.

Tataro et al.(31) demonstrated the association between high serum ALT level and more rapid development of HCC in patients with hepatitis C associated cirrhosis as 71.4% of patients in the high ALT group compared to 25% of patients in low ALT group developed HCC over a follow up period of more than 5 years. (31)

BCLC staging system was used to stage patients with HCC in group I. Most of the cases (56.6 %) were Stage B, 26.7 % of cases stage C, 10 stage A and 6.7 % stage D. Our results are comparable to Ikeda et al. multivariate analysis of HCC patients where most of the patients (51%) were in stage B. (32) This shows that early (stage A) HCC is rarely detected (due to lack of symptoms) as the case with late stages (as the symptoms must have appeared).

The recognition of specific genotypes of HCV is useful in studying the epidemiology, clinical manifestations and pathogenesis of disease. Sequential studies for the detection of the emerging of HCV mutants during the course of the disease may be necessary to understand the role of genotype variants in disease progression. (33)

Data regarding the role of viral genotypes in predicting long-term sequelae are contradictory and incomplete. Most efforts have focused on a comparison between those infected with genotype 1 and genotype 2 (34,35) or genotype 1b and 1a, (36) finding the former to be associated with more severe disease than the latter. Despite the fact that HCV genotype 4 is sometimes found in Europe, this genotype is the predominant one in the Middle East and Africa, excluding the republic of South Africa. (37-39)

In the present study we used INNO LiPA HCV II for genotyping of patients blood samples from all patients in both groups. It allows the discrimination of six HCV genotypes from 1 to 6 and 17 subgenotypes; 1a, 1b, 2a, 2b, 2c, 3a, 3b, 3e, 3a, 3b, 4a, 4b, 4c, 4d, 4e, 4f, 5a, 5b, 6a. Our results revealed that all patients in both groups (100 %) had genotype 4 HCV with no recognized subgenotypes.

Yates et al. found that 96% (74 of 77) of the Egyptian HCV strains among HCC cases were genotype 4. (40) This is consistent with report by McOnish et al. who found that genotype 4 is the predominant in Egypt.

Other authors reported the prevalence of genotype 4a in Egypt; Halim et al. (9%) (41) and Angelico et al. (12%) (42) In the former study the genotype was identified by type specific primers PCR technique, while in the latter study they used the first version of INNO-LiPA HCV, which is a line probe assay that discriminates five HCV genotypes (1-5) and 8 subgenotypes; 1a, 1b, 2a, 2b, 3a, 3b, 4a and 5a.

In our study, viral loads of HCV which indicate the activity of viral replication were significantly higher in group I (HCC patients) and increased with the stage of the disease. The loads in more advanced stages were higher.
than in early stages and considerably higher than loads in control group which indicates that the virus gets more aggressive as the condition deteriorates. These results agreed with Kato et al.\(^3\) study where the Viral loads of patients with late stages of HCC (C and D) were significantly higher than earlier stages (A and B).

Importance of Viral loads comes from being a variable quantity during disease progression; it can be the focus of larger trials testing its use as a predictor for malignant transformation in patients with HCV.

Sequence Analysis of 5'-untranslated region of HCV (5'UTR) was done to 8 RNA PCR extracts (4 samples from each group) using BigDye Sequencing Kit and ABI 377 DNA sequencer (ABI, USA), to check for a specific pattern of the 5'UTR of HCV (genotype 4) in the HCC patients that is different from the control group. Our aim was to check if there is a detectable mutation in the HCC group HCV that may be a risk factor for acceleration of development of HCC.

Phylogenetic analysis and sequence alignments of the 8 samples were plotted based on Nucleotides and deduced aminoacid sequences using CLUSTALW (1.82).The result of the comparison of the 8 DNA sequences from both groups showed that the 5'UTR were similar and there was no mutation present in group I characterizing the virus, different from group II.

However, two sequences (sample 4 from group I and sample 6 from group II) showed similarity less than 97% with the other 6 sequences while showing similarity of 97% or more to each other; they were gathered in one ancestor. This indicates that these two sequences may be considered as a new subgenotype from Genotype 4 that is present in Egyptian patients. Confirmation of such results needs more research with larger number of patients.

**Conclusions**

Genotype 4 is the predominant genotype of HCV in the studied patients. Viral loads of HCV may be used to monitor development of HCC. Subtypes of HCV genotype 4 identified need further work on larger scale. Serum GGT rather than AST and ALT can be used as a sensitive biochemical marker of hepatic dysfunction in patients with HCC. Further studies with large number of patients are needed to confirm these findings.

**Authors' Disclosures of Potential Conflicts of Interest:** The authors indicated no potential conflicts of interest.

**References**


Hepatocellular Carcinoma: Review of Clinicopathologic Features, Prognostic Factors and Treatment Results

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Key words: Hepatocellular carcinoma, clinicopathologic features, prognostic factors, treatment results.

ISSN: 2070-254X

Abstract

Background: HCC is the fifth most common cancer in the world, and the third most common cause of cancer-related death. In USA, the rate of HCC has increased by 70% over the last two decades. In Egypt, there is a remarkable increase in the incidence of HCC among patients with chronic liver disease from 4.0% to 7.2% over a decade.

Aim of the work: to discuss the clinicopathologic features, prognostic factors and treatment results of cases of HCC.

Patients and methods: 482 patients with HCC, from Damanhour Cancer Center and Behera Health Insurance between 2002 and 2006. Diagnosis by a biopsy or triphasic CT abdomen plus elevated AFP ≥ 400 ng/ml. Files of patients were reviewed for clinicopathologic features, treatment, prognostic factors, PFS and OS.

Results: Mean age 52.9 years. Male to female ratio 4:1. Most of patients (80.70%) were HCV positive; 77.2 % had Childs’-Pugh scores B/C. Tumor was solitary in 57.5% of patients. PV thrombosis was present in 20% of cases. Eighty six % of patients had elevated AFP > 400 ng/ml. Most patients presented in a late stage; 38.3% had BCLC stage C. 15.4 % of patients treated with potentially curative intent: surgery, RFA, TACE or conformal RT. Palliative treatment included RT, chemotherapy, hormonal, immunotherapy and best supportive care. CR was achieved in all patients treated by surgery. RFA achieved response rate (CR+PR) of 87%. TACE 75%, conformal RT 68%. Significant prognostic factors included: degree of hepatic cirrhosis, number of lesions, stage and portal vein thrombosis.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide. Its incidence is rising in part due to high incidence of Hepatitis C viral infection (HCV). In USA, the rate of HCC has increased by 70% over the last two decades. Registry data in Canada and Western Europe show similar trends.

In Egypt, there is a significant annual increase in the number of patients diagnosed with HCC. The rate rose from 4.0% of all cancers in 1993 to 7.2% in 2002. The most predominant age group is between 40 years and 59 years, with a significant male predominance (7 : 1).

Hepatocellular carcinoma is a disease with a dismal outcome. Most of the patients are presented with advanced disease and have a poor survival. It is a multicentric disease specially when associated with HCV.

The management of HCC is complex, because of numerous options that exist for treatment and the underlying liver disease. Early stage tumors can be managed using a variety of treatment modalities, including surgical resection, liver transplantation, radiofrequency ablation, local injection therapies and radiotherapy.

Surgical resection is still currently considered as the first choice of treatment for localized solitary resectable HCC. This is associated with the best outcome with 5-year survival exceeding 70% in Japan.

Liver transplantation is an effective option for patients with HCC corresponding to Milan criteria (solitary lesion less than or equal to 5cm or up to 3 nodules each less than 3 cm), in these selected patients the 5 year survival may exceed 70%.

Transarterial Catheter Chemoembolization (TACE) with lipiodol and chemotherapy is recommended as first line palliative therapy for non-surgical patients with large multifocal HCC who do not have vascular invasion or extrahepatic spread.

Radiofrequency ablation (RFA) is an appropriate therapeutic method for inoperable small tumors (less than 3 cm), deep within hepatic parenchyma and away from the hilum. Randomized controlled trials (RCT) have shown that radiofrequency ablation provides good local control that could result in an improved survival.

Conventional external beam radiotherapy had a limited role in the management of unresectable HCC, due to limited radiotolerance of the liver.

The use of three-dimensional (3D) conformal Radiation Therapy (RT) is promising.

For advanced and metastatic HCC, there are many options aiming mainly for palliation including hormonal therapy, systemic chemotherapy, novel targeted agents, and best supportive care in patients with poor performance status.
Aim of the work

Analysis of the clinicopathologic features, treatment results and prognostic factors of cases of HCC, seen at Damanhour Cancer Center and Behera Health Insurance.

Patients

The study included retrospective review of 482 patients who were diagnosed as having hepatocellular carcinoma (HCC), seen at Damanhour Cancer Center and Behera Health Insurance in the period between January 2002 and December 2006. Approval by Ethics Committee was obtained. Inclusion criteria included any age, any sex, pathologic diagnosis of HCC by a biopsy or clinical diagnosis by Triphasic CT of the abdomen plus elevated alpha-fetoprotein ≥ 400 ng/ml. Patients with incomplete criteria for diagnosis were excluded from the study.

Methods

The files of all patients (482 cases) were reviewed for the clinicopathologic features including:

- History and clinical findings.
- Pathologic criteria of the tumor, including the type and grade.
- Radiological features of the tumor, as detected by CT or Ultrasonography.
- Laboratory investigations including CBC, ALT, AST, serum Albumin, Bilirubin (total and direct), prothrombin time, viral markers (HBsAg, Anti-HCV Ab), alpha-fetoprotein and kidney functions.
- Staging of the disease according to BCLC staging system.\(^\text{22}\)
- Treatment modalities received, and treatment response.
- Progression- free survival (PFS) and overall survival (OS).

Results

There was a gradual increase in the number of diagnosed patients with HCC since 2002. Around 40% of the studied patients (212/482) were referred to Oncology at only one year (2006). The age ranged between 20 and 80 years with a mean age of 52.9 years and the peak incidence was among the age group (50 - < 60 y). Three hundred and ninety two patients (81.3 %) were males and 90 patients (18.7 %) were females, with male to female ratio of around 4:1. Forty four percent of patients had ECOG performance status (\(^\text{23}\)) of 0-1, while 17% had ECOG scale 4. The majority of patients (80.70 %) were HCV positive. Liver functions assessment was done using Childs'-Pugh scoring. (\(^\text{24, 25}\)) The majority of patients (77.2 %) had Childs'-Pugh scores B and C at presentation; while only 22.8% had score A. (Table 1)

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - &lt; 30</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>30 - &lt; 40</td>
<td>11</td>
<td>2.0</td>
</tr>
<tr>
<td>40 - &lt; 50</td>
<td>82</td>
<td>17.0</td>
</tr>
<tr>
<td>50 - &lt; 60</td>
<td>204</td>
<td>43.0</td>
</tr>
<tr>
<td>60 - &lt; 70</td>
<td>118</td>
<td>24.4</td>
</tr>
<tr>
<td>70 - 80</td>
<td>64</td>
<td>13.0</td>
</tr>
</tbody>
</table>

Table (2) shows different initial clinical presentations of the studied patients. The most common clinical presentations were right hypochondrial pain (60%) and symptoms due to metastases (42%). Thirty eight percent of patients presented by abdominal distention (ascites). Jaundice was detected in 20% of patients. Interestingly, 12% of patients were asymptomatic at presentation.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>No. of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rt. hypochondrial pain</td>
<td>289 / 482</td>
<td>60 %</td>
</tr>
<tr>
<td>Symptoms related to metastases</td>
<td>202 / 482</td>
<td>42 %</td>
</tr>
<tr>
<td>Abdominal distension (ascites)</td>
<td>188 / 482</td>
<td>38 %</td>
</tr>
<tr>
<td>Lower limb edema.</td>
<td>173 / 482</td>
<td>36 %</td>
</tr>
<tr>
<td>Dyspepsia.</td>
<td>144 / 482</td>
<td>30 %</td>
</tr>
<tr>
<td>Malaise.</td>
<td>115 / 482</td>
<td>24 %</td>
</tr>
<tr>
<td>Epigastric pain.</td>
<td>96 / 482</td>
<td>20 %</td>
</tr>
<tr>
<td>Jaundice.</td>
<td>96 / 482</td>
<td>20 %</td>
</tr>
<tr>
<td>Bleeding.</td>
<td>77 / 482</td>
<td>16 %</td>
</tr>
<tr>
<td>Weight loss.</td>
<td>67 / 482</td>
<td>14 %</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>57 / 482</td>
<td>12 %</td>
</tr>
</tbody>
</table>

The most common sites of metastases at presentation were: bone (37%) and lymph nodes (porta hepatic and para-aortic) (21%). Other sites included lung (11%), subcutaneous tissues (7%) and supra-renal glands (6%). Eighteen percent of patients presented by multiple sites of metastases.

Diagnosis of HCC was based mainly on radiologic imaging (triphasic CT), serologic tests (serum level of AFP) and biopsy. Triphasic CT abdomen and pelvis was the standard radiologic imaging technique for diagnosis in all cases. The majority of patients (59.3%) had tumors located in the right lobe of the liver, 20.7% had left lobe tumors and 20% had tumors in both lobes. The tumor was solitary in 57.5% of patients and multicentric in 42.5% of them. Moderate degree
of cirrhosis was detected in almost three quarters of patients (74.6%). Portal vein thrombosis was present in 98 cases (20%).

The majority of patients (96.6%) had elevated level of AFP; 86% had AFP ≥ 400 ng/ml (the diagnostic cut-off point), while 10.6% had AFP level < 400 ng/ml. On the other hand, only 3.4% had normal levels of AFP. Among 482 patients with HCC, only 105 patients underwent biopsy. The most common pathological type was moderately differentiated HCC (grade II) which was reported in 72.4% of patients. Clear cell type was detected in only 3 patients (2.8%). Diagnosis of HCC was made by combination of radiological, serological tests and/or biopsy. (Table 3).

Staging of patients was done using BCLC staging system. Most of the patients were presented in a late stage; 38.3% had stage C and 24.7% had stage D; while stages A 17.2 % and B 19.8 %.

Seventy-four patients were treated with potentially curative intent. Seventeen patients underwent surgery, 24 patients had RFA, 8 had TACE and 25 had conformal radiotherapy. These patients had small single tumors, good performance states (ECOG scores 0-2) with excellent liver functions (Childs’-Pugh scores A and B). The rest of the patients (408) were treated with palliative modalities (4 patients). Palliative treatment included palliative RT (14 patients), management of ascites. (Table 4)

All patients were assessed for response by clinical examination, laboratory investigations including serum AFP and radiologic imaging by U/S and triphasic CT abdomen and pelvis. Complete tumor eradication (CR) was achieved in all patients treated by surgical resection. Surgery had a minimum relapse-free survival of 6 months, a maximum of 45 months and a median of 26 months. RFA achieved response rate (CR+PR) of 87% with a relapse-free survival duration range of 6 – 14 months and a median of 10 months. Patients treated by TACE achieved response rate of 75% and relapse-free survival duration range of 4 – 12 months with a median of 8 months. On the other hand, conformal radiotherapy achieved response rate of 68% with relapse-free survival range of 8 – 16 months and a median of 12 months.

Palliative RT was applied to 14 patients for pain relief or relief of obstructive jaundice due to enlarged porta hepatis nodes. Forty-two percent of the patients achieved stable disease (SD) with progression-free survival ranged from 2–6 months with a median of 4 months. RFA achieved response rate (CR+PR) of 87% with a relapse-free survival duration range of 6 – 14 months and a median of 10 months. Patients treated by TACE achieved response rate of 75% and relapse-free survival duration range of 4 – 12 months with a median of 8 months. On the other hand, conformal radiotherapy achieved response rate of 68% with relapse-free survival range of 8 – 16 months and a median of 12 months.

The overall survival (OS) of the whole group ranged from 2 – 48 months with a mean of 9.96 months; while the progression-free survival (PFS) ranged from 1 week – 45 months with a mean of 4.03 months. (Figures 1, 2)

### Table 3: Diagnostic findings.

<table>
<thead>
<tr>
<th>Level of AFP</th>
<th>No. of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (0-10 ng/ml)</td>
<td>16</td>
<td>3.4</td>
</tr>
<tr>
<td>Elevated &lt; 400 ng/ml</td>
<td>51</td>
<td>10.6</td>
</tr>
<tr>
<td>Elevated ≥ 400 ng/ml</td>
<td>415</td>
<td>86.0</td>
</tr>
<tr>
<td>Total</td>
<td>482</td>
<td>100.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biopsy findings</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC grade 1</td>
<td>11</td>
</tr>
<tr>
<td>HCC grade 2</td>
<td>76</td>
</tr>
<tr>
<td>HCC grade 3</td>
<td>15</td>
</tr>
<tr>
<td>Clear cell type</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic modalities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Triphasic CT + AFP ≥ 400 ng/ml</td>
<td>377</td>
</tr>
<tr>
<td>Triphasic CT + biopsy</td>
<td>73</td>
</tr>
<tr>
<td>Triphasic CT + AFP ≥ 400 ng/ml + biopsy</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td>482</td>
</tr>
</tbody>
</table>

### Table 4: Different treatment modalities.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially Curative:</td>
<td>74/482</td>
<td>15.4</td>
</tr>
<tr>
<td>Surgery</td>
<td>17</td>
<td>3.5</td>
</tr>
<tr>
<td>RFA</td>
<td>24</td>
<td>5.0</td>
</tr>
<tr>
<td>TACE</td>
<td>8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Fig 1: The overall survival (OS) of patients.

- Mean = 9.96 months, Median = 8.0 months

Mean = 9.96 months, Median = 8.0 months
Patients treated by surgery had the best mean OS and PFS. Patients who underwent surgery, conformal RT, TACE and RFA had mean OS of 24.89, 17, 14 and 13.95 months respectively with statistically significant difference (p= 0.002) and mean PFS of 17.56, 11.48, 9.86 and 9.50 months respectively (p = 0.016).

Discussion

The incidence of HCC in Egypt had increased since the year 2002 and reached a peak at 2006. This rising may be explained by increased risk factors as well as improvement of the screening programs and diagnostic tools of HCC. Modern therapy has led to increased survival among cirrhotic patients with HCV infection that allowed time for development of HCC.

Our results showed that HCC was more prevalent in men than in women, with male to female ratio of 4:1. This was consistent with the findings of Kasahara et al., where men were at 4.35 times risk to develop HCC than women.(26) This may be attributed to differences in exposure to risk factors.(2) However, it had been speculated that estrogens and androgens could modulate hepatocarcinogenesis and explain the higher incidence of HCC in men.(27)

Analysis of the age distribution among HCC patients revealed that the most predominant age group was 50 to < 60 years which included 42% of the patients. Eighty percent of cases were ≥ 50 years and the ratio between patients ≥ 50 years and those < 50 years was 4 : 1. This is consistent with results of Velazquez et al. who found that cirrhotic patients older than 54 years were at four times greater risk to develop HCC. (28)

Thirty seven percent of patients had ECOG scale 0 while 31% had ECOG scale 2. On the other hand, 17% of cases presented by ECOG scale 4. The relatively good performance status may be explained by improvement in screening and diagnostic methods that facilitated early detection of cases.

Anti- HCV antibodies were positive in 80.70 % of the patients. This agreed with Nishioka et al. from Japan who showed that 76 % of HCC cases were HCV positive.(29) Bosch et al. indicated that the rise in the incidence of HCC was directly related to the increase in the prevalence of HCV infection.(30) This is also consistent with Sun CA et al, who illustrated that HCV positivity conferred a 20-fold increased risk of HCC compared to HCV negative patients.(31)

The most common clinical presentation among patients was right hypochondrial pain (60 %) which may be explained by the location of the tumor in the right lobe of the liver in 59.3 % of cases. On the other hand, about 30% and 20% of patients had experienced dyspepsia and epigastric pain respectively (p = 0.001). The presence of portal vein thrombosis had a significant adverse effect on both OS and PFS. The mean OS was 10.54 and 7.83 months in patients without and with portal vein thrombosis respectively (p < 0.001).

Increasing number of HCC lesions had a negative impact on OS; The mean OS among patients with single and multiple lesions were 10.79 and 8.78 months respectively (p<0.001). Patients with single lesions had better 1y and 2y survival rates than those with multiple lesions (p = 0.010).

Right lobe lesions had the best mean OS of 10.50 months as compared to 10.09 and 8.13 months in Left lobe and both lobes lesions respectively (p = 0.004); moreover, the mean PFS was 4.26, 4.16 and 3.16 months in right, left and both lobes lesions respectively (p = 0.013). Two year survival rate was significantly better in right Lobe lesions than left lobe or both lobes lesions (p=0.036).

Patients with BCLC stages A, B, C and D had mean OS of 17, 10.57, 8.36 and 5.98 months respectively (p < 0.001) and mean PFS of 5.58, 5.0, 3.66 and 2.40 months respectively. (p < 0.001). One year and 2y survival rates were significantly higher (p < 0.001) in lower stages.

Patients with mild, moderate and severe cirrhosis, had mean OS of 9.63, 10.80 and 11.03 months respectively (p = 0.013). Two year survival rate was significantly higher (p < 0.001) in lower stages.

The mean OS of patients less than 50 years and those ≥ 50 years was 8.78 and 10.25 months respectively with no statistically significant difference (p=0.004); moreover, the mean PFS was 4.26, 4.16 and 3.16 months in right, left and both lobes lesions respectively (p < 0.001). Two year survival rate was significantly higher (p < 0.001) in lower stages.

The relation between clinicopathological features of patients and survival was studied. The age of patients had no significant impact on OS, PFS, 1 year (1y) or 2 year (2y) survival rates. The mean OS of patients less than 50 years and those 50 years or more was 8.78 and 10.25 months respectively with no statistically significant difference (p=0.059). Sex also had no significant impact on survival. The mean OS was 9.71 and 11.03 months in males and females respectively (p=0.078). The mean PFS among patients with ECOG scales 0, 1, 2, 3 and 4 were 4.58, 5.14, 3.95, 3.74 and 3.37 months respectively with statistically significant difference (p=0.045). ECOG scale also had a statistically significant impact upon both 1-y and 2-y survival rates. HCV positive patients had significantly lower 1y and 2y survival rates.

Progression-free survival among patients with Childs'-Pugh scores A, B, C and D had mean OS of 17, 10.57, 8.36 and 5.98 months respectively (p=0.001). Moreover, liver functions as assessed by Childs'-Pugh scores had a statistically significant impact on both 1-y and 2-y survival rates. Level of AFP had a significant impact on both 1y and 2 y survival rates. (p=0.005)

Degree of hepatic cirrhosis affected significantly both OS and PFS. Patients who had mild, moderate and severe cirrhosis, had mean OS of 9.63, 10.80 and 7.18 months respectively (p<0.001).

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hepatitis or cirrhosis. Levels above 400 ng/ml had positive predictive value for HCC of > 60%. In this study, elevated level of AFP was detected in 96.6% of patients while diagnostic AFP level (≥ 400 ng/ml) was detected in 86%. Bruix et al published that the level of AFP was elevated above normal in only 60 – 70% of HCC cases. The difference may be attributed to the increasing adoption of HCC screening program as well as the use of more sensitive assay methods over the recent years.

Because of late stage presentation, most of our patients (84.6%) were treated with a palliative intent; only 3.5% had undergone curative surgery. Local treatment (RFA, RT, TACE) was given to 11.9% of patients.

All patients who underwent surgery achieved complete remission due to complete resection of the disease. RFA came in the 2nd order where 58% of cases had CR. This result was inferior to that obtained by Lencioni et al, where RFA was superior to per-cutaneous ethanol injection (PEI) in local recurrence-free survival rates. Complete tumor response was achieved in 91% of HCCs treated with RFA with an average of 1.1 treatment sessions, but only in 82% of HCCs treated with PEI with an average of 5.4 treatment sessions.

TACE was the 3rd for treatment response in the current study where 25 % of patients achieved CR. This result was better than that of Llovet et al. where significant tumor response was achieved in 17%– 61.9%, but CR was rare (0%– 4.8%) since viable tumor cells remain after TACE.

Sixty eight percent of patients who received conformal radiotherapy achieved objective response (CR+PR). These results were superior as compared to those of a study done at the University of Michigan, where conformal RT has been used with concurrent hepatic arterial fluorodeoxyuridine as a radiosensitizer for the treatment of primary and metastatic liver cancers. Tumor received doses up to 90 Gy in 1.5 Gy per fraction, twice daily, with an objective response of 56%.

Dawson et al., on the other hand, reported the same objective response rate we achieved; 68% (16 PR and 1 CR). They delivered a median dose of 58.5 Gy (range 28.5 to 90 Gy), 1.5 Gy per fraction, twice a day with concurrent hepatic arterial infusion of FUDR.

Palliative chemotherapy in the form of 5-fluoro-uracil/ leucovorin or adriamycin as a single agent had led to PR in 11 % of patients with mean progression-free survival of 10 months. This response to chemotherapy was inferior as compared to Leung et al. work in which 50 patients treated with 1.V chemotherapy PIAF (cisplatin, interferon-alpha, doxorubicin, and 5-fluorouracil). The PR was 26% and 4 patients achieved CR. The difference may be due to higher efficacy of combination chemotherapy and/or the inclusion of interferon-alpha.

Palliative RT with total doses of (21 – 30 Gy) in 3 Gy per fraction kept the disease stable in 42 % of patients with pain relief and improved quality of life. The median PFS was 4 months. This was comparable to several studies using the same dose range, associated with pain relief and stable disease in almost half of patients with improvement in liver function tests. Overall, the median survival was short (3-9 months) and death was usually due to progression of disease.

Hormonal therapy in the form of tamoxifen achieved stable disease in 29 % of patients; this was consistent with other trials showing no objective response to tamoxifen, or the antiandrogen ketoconazole.

Hepato-cellular carcinoma is a grave disease with short overall survival. In a retrospective study done by A. Martins and H. Cortez-pinto published in 2006, the median OS was 24 months which was comparable to other retrospective European studies. On the other hand, a recent population-based study of the extent and determinants of HCC therapy in the United States revealed a much poorer prognosis with a median survival of only 104 days following HCC diagnosis. In the present work, the mean OS was 9.96 months.

This may be explained by prevalence of cirrhosis and late stage at presentation.

Patients’ age and sex had no significant impact on survival; which is comparable to the Japanese study by Wang et al. where both age and sex had no relation to survival. However, performance status according to ECOG scale had significant impact on both 1 and 2-year survival rates.

Patients with negative anti-HCV antibodies had significantly better 1 and 2-year survival rates. This was in disagreement with a study conducted in Japan by Masafumi Ikeda et al. that stated that HCV sero-positivity was a good prognostic factor. This might be explained by association with favorable tumor-related factors in their study, such as smaller tumor size and numbers.

Liver functions presented by Childs’-Pugh chart had a significant impact on PFS where patients with Childs’-Pugh chart A had better PFS than patients with charts B and C (p=0.001). Inspite of not having significant impact on OS, patients with Childs’-Pugh chart A had better 1 and 2-year survival rates (p< 0.001). This is consistent with Sala et al. who stated that liver functions as per Childs’-Pugh chart was among the most important predictors of survival.

AFP level had no significant impact on both OS and PFS; which was comparable with a study done by A. Martins et al. published in 2006 and concluded that level of AFP was not a predictor for survival in HCC. However, subanalysis revealed that patients with normal or elevated AFP level < 400 ng/ml had significantly better 1 and 2-year survival rates than those with AFP level of ≥ 400 ng/ml. This was consistent with the Japanese study which stated that patients with AFP level ≥ 400 ng/ml had 30% shorter survival.

Another study published in British journal of cancer in 2008 supported this result.

The poor prognosis of patients with elevated AFP may be due to correlation with tumor burden. In addition, it was reported that poorly differentiated HCC produce more AFP. Therefore, higher AFP levels usually reflect a more advanced stage and greater malignant potential of tumors.

Portal vein thrombosis, which is also a reflection of the biologic aggressiveness of the tumor had a significant adverse effect on patients’ survival; results consistent with the Japanese study.

Multiplicity of lesions had a significant adverse effect on overall, 1-year and 2-year survival rates. Many published studies showed similar results as the Japanese study by Masafumi Ikeda et al. and the study by K Noso et al. This can be explained by reduced volume of normal liver which is usually cirrhotic with deteriorated function.

Patients with right lobe tumors had significantly longer OS than those with left lobe and both lobes; same finding was seen in the Japanese study by Masafumi Ikeda et al. Tumors in the Lt. lobe usually produce epigastric pain and dyspepsia so, could be misdiagnosed as gastritis or colonic disturbance with delayed diagnosis. Bilateral tumors are usually associated with small volume of remaining normal liver with low hepatic reserve and impaired liver functions.

As in many other cancers, tumor stage (BCLC) had a significant impact on overall, progression-free, 1-year and 2-year survival rates. Patients with BCLC stage A had the best OS, while patients with stage D had the worst OS (p < 0.001). Zaigham et al. also reported that BCLC stage is an important predictor of survival in HCC.

The type of therapy applied to HCC patients whether curative or locoregional had a significant impact on both PFS and OS. Surgery as a curative line of therapy applied to early stage HCC had the best mean overall survival of 24.89 months. Unexpectedly, RT came in the 2nd order in prolongation of patients’ survival; this might be due to modern advances in delivery of higher doses of RT which is more conformal with more sparing of normal liver tissue and organs at risk. TACE is the only method proven to have survival benefit in phase III studies. In the present study, it came in the 3rd order. Patients who underwent RFA had the least overall survival which might be due to high recurrence rate.
Conclusions

HCC is a grave disease with a dismal outcome and short overall survival. Its incidence has increased in Egypt mostly due to high prevalence of HCV infection. Most of the patients are presented in late stages. Patients at high risk to develop HCC should be entered into surveillance programs for early detection. Surgical resection is the best curative treatment modality in early cases. Among palliative treatment methods, chemotherapy is better than radiotherapy and immunomodulation in achieving response. Significant prognostic factors include: degree of hepatic cirrhosis, number of lesions, stage and portal vein thrombosis. Large randomized clinical trials are needed to confirm these findings.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST:
The authors indicated no potential conflicts of interest.

References

Cost utility considerations with new radiotherapy modalities

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Key words: Radiotherapy, cost utility, cost effectiveness.

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Abstract

Despite the recent advances in cancer biology and therapeutics, cancer control is still a difficult job and implementation of newer radiotherapy modalities could help advance our war against this lethal disease while minimizing the incidence of treatment-related morbidities.

However, wide implementation of such high tech radiotherapy techniques has grave economic consequences that should be dealt with cautiously and scientifically with detailed cost utility/effectiveness analyses to properly employ limited health care resources in low/middle income countries.

Cancer care is expensive

The economic burden of cancer is the largest imposed by any medical illness. The high expense associated with cancer is related to a number of factors, including an increase in the prevalence of cancer as people live longer, the high rate of comorbid medical illness in cancer patients, and high costs associated with diagnosis, treatment, and end-of-life and palliative care as new, more expensive treatments become available(1). Cost is a major determinant of the type and intensity of cancer care, particularly related to reimbursement of high-tech and high-cost procedures and pharmaceutical products for cancer patients. The physician has a large role in determining the medical costs incurred by individual patients (8).

It is obvious that not all medical novelties can be offered to all patients. Each pound can be spent only once, and investment into one treatment therefore often is a decision against another, perhaps better approach. Enthusiasm for a novel technology should be the basis for its scientifically sound, academic evaluation but not be the basis for its general introduction into routine clinical practice (13).

Considerations in Delivery of Radiation Therapy in Low- and Middle-Income Countries

Challenges to delivering cancer control and radiation therapy in limited-resource settings may include lack of cancer awareness and knowledge among health care workers and the public, lack of diagnostic and treatment equipment and infrastructure, limitations in referral systems, challenges due to geography and population distribution, and inadequate cancer registry data. Often there can be a mismatch between resources and need, and the nature of this varies. For instance, there may be insufficient human resources but fair equipment supply, or adequate brachytherapy equipment but inadequate supply of teletherapy equipment. In addition, there is an overall shortage of health care workers in many countries in the developing world that limit available trainees for radiation oncology and other specialties (2).

Types of Economic Analyses

Cost-effectiveness analysis provides information about the value of an intervention or therapy in relation to its costs compared to a competing alternative when effectiveness is measured in clinical terms. The analysis compares two or more interventions and provides information about the differences in costs and effects between comparators. Whereas cost-utility analysis is a subset of cost-effectiveness analysis in which the measure of effectiveness is a utility or value.

Utilities provide a measure of overall quality of life and are applicable across different types of cancer (1,3).

Examples of cost effectiveness and cost utility analyses with different modern radiotherapy techniques:

1- Particle beam therapy
Proton beam therapy has been in use for many decades; although its theoretical benefits are not in doubt, there is remarkably little published data strongly supporting its use over other forms of radiation, with the exception of ocular and skull-base tumors and malignancies of children. However, these cancers are rare and the patient demand would be insufficient for new proton therapy centers (4).
Currently, proton therapy is undergoing transitions that will move it into the mainstream of cancer treatment. For example, proton therapy is now reimbursed, there has been rapid development in proton therapy technology, and many new options are available for equipment, facility configuration, and financing. During the next decade, new developments will increase the efficiency and accuracy of proton therapy and enhance our ability to verify treatment planning calculations and perform quality assurance for proton therapy delivery. With the implementation of new multi-institution clinical studies and the routine availability of IMPT (intensity modulated proton therapy), it may be possible, within the next decade, to quantify the clinical gains obtained from optimized proton therapy. During this same period several new proton therapy facilities will be built and the cost of proton therapy is expected to decrease, making proton therapy routinely available to a larger population of cancer patients (5).

The current literature on cost-effectiveness of particle therapy is scarce, non-comparable, and largely not performed according to standard health technology assessment criteria. Besides, different perspectives for cost evaluations have been used, making it difficult to compare and to determine the relative impact in terms of costs for this new treatment modality. Evidence on the cost-effectiveness of particle therapy is scarce. Adequate reimbursement is necessary to support such innovative yet costly treatments (7).

A systematic literature review of the clinical and cost-effectiveness of hadron (i.e. neutron, proton and light or heavy ion) therapy (HT) in cancer was done by Lodge and colleagues. Seven hundred and seventy three papers were identified. For proton and heavy ion therapy, the number of randomized trials was too small to draw firm conclusions. Based on prospective and retrospective studies, proton irradiation emerges as the treatment of choice for some ocular and skull base tumors. For prostate cancer, the results were comparable with those from the best photon therapy series. Heavy ion therapy is still in an experimental phase. So, Existing data do not suggest that the rapid expansion of HT as a major treatment modality would be appropriate (6).

2- 3D conformal radiation therapy:

Three-dimensional conformal radiation therapy (3DCRT) is a sophisticated technique that allows high doses of radiation to be focused safely on a target. This technique is more expensive to implement and deliver compared with conventional radiation techniques. A consensus, however, is emerging after reviewing the data that shows three-dimensional conformal radiation therapy to be cost-effective when the clinical benefit is most apparent (9).

The cost effectiveness considerations of 3DCRT have been discussed in a number of disease sites particularly in cancer prostate. Poon and colleagues have discussed this subject, activity based costing has been used to create a model of radiotherapy related costs for prostate cancer. A process map was developed which separated the process in five activities for conventional radiotherapy and six activities for dose escalated conformal radiotherapy. The majority of the cost differences arose from the cost of the additional time needed for treatment per day as well as the extra fractions per patient when compared to conventionally treated patients. The average treatment times per fraction for six field conformal, four field conformal and four field conventional have the median times of 22.72, 20.63 and 11.07 minutes respectively. Planning costs for conformal radiotherapy were up to three times the cost of conventional therapy. The direct costs of dose escalated conformal external beam radiotherapy are over 2.5 times that of conventional external beam radiotherapy for early stage prostate cancer. These direct costs are a reflection of the additional capital and human resources needed to provide state-of-the-art radiation therapy.

3- Intensity modulated radiation therapy:

Intensity-modulated radiotherapy (IMRT) is a newer method of radiotherapy that uses intensity-modulated beams that can provide multiple intensity levels for any single-beam direction and any single-source position, allowing concave dose distributions and dose gradients with narrower margins than those possible using conventional methods. IMRT is ideal for treating complex treatment volumes and avoiding close proximity organs at risk that may be dose limiting and provides increased tumour control through an escalated dose and reduces normal tissue complications through organ at risk sparing (19).

The impact of learning effects on the variability of costs of new health technologies in a prospective payment system (PPS) through the case of intensity modulated radiation therapy (IMRT) was studied by a series of consecutive patients treated in nine medical centers was enrolled in a prospective study. Direct costs were assessed from the perspective of the healthcare providers. Two-level model was used to explain the variability of costs; patients nested within centers. The authors reached the conclusion that learning effects are a strong confounding factor in the analysis of costs of innovative health technologies involving learning effects. In a PPS, innovative health technology involving learning effects necessitates specific reimbursement mechanisms (11).

And in another French study, an economic evaluation of intensity modulated radiotherapy (IMRT) in head and neck cancer was carried out to assess the cost of treatment and compare it to reimbursement paid to hospitals in the French Prospective Payment System. Planning required in average 20 hours of work for the physician and 6 hours for the radiation oncologist. Radiation consisted of 33 fractions in average and required 29 hours of work for the radiotherapy technician, 8 hours for the physician and 3 hours for the radiation oncologist. As more patients were treated, unit cost of treatment was decreasing. In the French Prospective Payment System, mean reimbursement of IMRT was $6,987. For 70 % of the patients, reimbursement did not offset the cost of treatment. A financial support for hospitals implementing the technique is essential during the whole learning period (12).

4- Image guided radiation therapy:

For IGRT as for all other developments in the field of radiation oncology, all patients should have guaranteed access to technological advances if they profit from this technology. Large and high quality prospective data bases, and models which relate details of the patient (if possible including tumour and normal tissue biobanking) with details of the treatment and detailed outcome parameters, are necessary for supporting rational decision making. For this it is a great advantage that radiobiology and radiotherapy are highly quantitative sciences and that radiation dose can be measured with great accuracy. The question whether the results were obtained from randomized trials or not will eventually lose much of its current attention if it can be demonstrated that the models in use can validly and reliably predict outcome, thereby supporting decision making and individualization of therapy (14).

5- Stereotactic irradiation:

As a minimal access surgical approach, stereotactic radiosurgery fits well into the patient goals of functional preservation, risk reduction, and cost-effectiveness. Longer-term results have been published for many intracranial as well as
extracranial indications. It can be performed alone when lesion volume is not excessive or as part of a multimodality strategy with resection or endovascular surgery. The combination of high-resolution imaging, high-speed computer workstations, robotics, patient fixation techniques, and radiobiological research has put radiosurgery into the practice of almost all neurosurgeons as well as neuro-oncologists. However, the issue of cost effectiveness –particularly in a limited resource setting- is very challenging (17).

A number of studies has been undertaken to analyze the cost effectiveness of innovative stereotactic irradiation techniques, of these a preliminary investigation of costs and quality of life (QoL) for two modalities [brachytherapy (BT) and robotic radiosurgery] used to boost radiation to the primary tumors following external beam radiotherapy was done. Quality of life (pain and difficulty swallowing) was established in long-term follow-up for patients undergoing BT and over a one-year follow-up in robotic radiosurgery patients. Total hospital costs for both groups were computed. Efficacy and quality of life at one year are comparable for BT and robotic radiosurgery. Total cost for robotic radiosurgery was found to be less than BT primarily due to the elimination of hospital admission and operating room expenses. The present study shows how a preliminary assessment of a new medical technology such as robotic radiosurgery with its typical hypofractionation characteristics might be based on short-term clinical outcomes and assumptions of equivalence (15).

And another cost-utility study evaluated the cost-effectiveness of cyberKnife stereotactic radiosurgery (SRS) in comparison to external beam radiation therapy in the treatment of metastatic spinal malignancies. Costs of care were derived from Centers for Medicare and Medicaid Services fee schedules. Because cancer therapies bear significant health and economic consequences, the impact of treatment-related toxicities was integrated into the analysis. Given the terminal nature of these conditions and the limited life expectancy of the patient population, the time horizon for the analysis was limited to 12 months. Cost-utility analysis demonstrated that cyberKnife SRS was a superior, cost-effective primary intervention for patients with metastatic spinal tumors compared with conventional external beam radiation therapy (16).

In another study, Cost-effectiveness analysis was done for trigeminal neuralgia regarding Cyberknife vs. microvascular decompression. Direct healthcare costs from hospital’s perspective attributable to Cyberknife and microvascular decompression were collected. The two procedures resulted equally effective at 6 month follow-up, with different resources consumption: Cyberknife reducing hospital costs by an average of 34% per patient. The robustness of these results was confirmed in appropriate sensitivity analyses. Cyberknife resulted to be a cost-saving alternative compared with the surgical intervention (18).

Conclusions

Despite the recent advances in cancer biology and therapeutics, cancer control is still a difficult job and implementation of newer radiotherapy modalities could help advance our war against this lethal disease while minimizing the incidence of treatment-related morbidities.

However, wide implementation of such high tech radiotherapy techniques has grave economic consequences that should be dealt with cautiously and scientifically with detailed cost utility/effectiveness analyses to properly employ limited health care resources in low/middle income countries. So conduct of cost effectiveness analyses for these newer techniques should be considered as a priority for academic institutes in the Arab region.

Disclosure: I have no conflicts of interest

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Denosumab in the treatment of bone metastasis from solid tumors

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Introduction

Bone is the most common site of metastatic disease in patients with solid tumors; it is the third common place for metastasis after lung and liver. Given the high prevalence of breast, prostate, and lung cancer, they are responsible for more than 80% of cases of metastatic bone disease. Patients with metastatic disease of the bone are at risk for skeletal-related events (SREs), which are defined as: pathologic fracture, spinal cord compression, and other complications related to skeletal involvement, including hypercalcemia of malignancy, radiation therapy to alleviate pain or prevent fracture or surgery to prevent or treat fracture. Thus SREs are a major source of morbidity for cancer patients and its prevention is a vital component of their oncologic care.

Since the 1990s, bisphosphonates have been the mainstay of treatment to prevent SREs in patients with cancer metastases to bone. They acting mainly through two ways: firstly by inhibiting continued bone resorption and secondly by induction of apoptosis (1).

Zoledronic acid is the first bisphosphonate approved for use in all solid tumor patients with bone metastases as well as in multiple myeloma. Despite optimal bisphosphonate therapy, 30%–50% of cancer patients with bone metastases still develop SREs while on bisphosphonate therapy (2, 3). In addition, there are concerning treatment-related side effects associated with its use, including gastrointestinal irritation, nephrotoxicity, osteonecrosis of the jaw (ONJ), and hypocalcaemia. Intravenous infusion of zoledronic acid can be associated with an acute-phase reaction, including bone pain, fever, and chills in up to 30% of patients as well as renal toxicity that is dose and infusion time dependent. It is not recommended for use in patients with a creatinine clearance lower than 30 mL/minute and with dose-modification if it is less than 60 mL/minute (4). Consequently, monthly monitoring of renal function is required prior to each dose. It is hypothesized that tumor cells in the bone lead to increased expression of receptor activator of nuclear factor kappa-B ligand (RANKL) on osteoblasts and their precursors. RANKL is an essential mediator of osteoclast function, formation, and survival (5-7). Excessive RANKL-induced osteoclast activity results in resorption and local bone destruction leading to SREs (8, 9).

The first available drug to target the RANK-RANKL pathway is denosumab, a fully human monoclonal antibody that specifically binds and neutralizes RANKL, thereby inhibiting osteoclast function. The initial Phase I trials demonstrated that osteoclastic activity is almost completely eradicated while denosumab is in circulation, however, the effect is reversible (10).

In the Phase III FREEDOM trial, 7868 postmenopausal women (aged 60–90 years) with osteoporosis were randomly assigned to subcutaneous denosumab (60 mg every 6 months) or placebo. After 3 years, denosumab improved bone mineral density compared with placebo and when compared with bisphosphonates; it has shown improvements in both bone mineral density and markers of bone loss (11).

The guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend bone mineral density testing with a dual-emission x-ray absorptiometry scan for postmenopausal women taking aromatase inhibitors and drug therapy for those with documented osteoporosis (12).

In a randomized, double-blind, placebo-controlled trial, 252 women with hormone receptor-positive, early-stage breast cancer treated with adjuvant aromatase inhibitor therapy were randomly assigned to receive placebo or subcutaneous denosumab 60 mg every 6 months. At 12 and 24 months, lumbar spine bone mineral density increased by 5.5% and 7.6%, respectively, in the denosumab group compared with the placebo group (P, 0.0001) (13).

In the HALT (Hormone Ablation Bone Loss) trial, 1468 men receiving androgen deprivation therapy for non metastatic prostate cancer were randomly assigned to denosumab (60 mg subcutaneously every 6 months) or placebo. Eligibility included male gender, age 70 years or, 70 years with baseline low bone mineral density (T score at the lumbar spine, total hip, or femoral neck of less than -1.0). At 24 months, denosumab was associated with increased bone mineral density at all measured sites (P, 0.001 for all comparisons) (14). The promising outcomes in the initial trials with denosumab in treatment-related osteoporosis associated with breast and prostate cancer led to exploration of its use for the prevention of skeletal-related events in patients with solid tumors and bone metastasis.

Doses

Denosumab has US Food and Drug Administration (FDA) approval at a dose of 60 mg subcutaneously every 6 months for the treatment of both primary osteoporosis and bone loss associated with aromatase inhibitor therapy in early-stage breast cancer and androgen deprivation therapy for nonmetastatic prostate...
cancer. At a dose of 120 mg subcutaneously every four weeks for the prevention of SREs in patients with bone metastases from solid tumors.

**Pharmacokinetics and Side effects**

Denosumab absorption is rapid and sustained, with a bioavailability of 62%, a steady-state mean serum concentration of 20.5 ug/mL, and an elimination half-life of 28 days. A decrease in bone resorption markers is observed within 24 hours after initial dose administration, and steady-state levels are achieved by 6 months following multiple doses at the 120 mg monthly schedule (15).

It is eliminated through the immunoglobulin clearance pathway via the reticuloendothelial system, is thus thought to be independent of renal or hepatic function (16). So no need to dose reduction or renal monitoring with denosumab therapy. However, there is a lack of safety data in patients with severe renal dysfunction because patients with creatinine clearance levels less than 30 mL/minute were excluded from the trials. No clear data about its use in patients with a creatinine clearance of less than 30 mL/minute or in those who are receiving dialysis. The risk of hypercalcemia is increased with chronic renal disease. To minimize this risk, Healthcare Professionals reminded the following:

- Pre-existing hypocalcaemia must be corrected prior to initiating therapy.
- Supplementation of calcium and vitamin D is required in all patients unless hypercalcemia is present.
- If hypocalcaemia occurs, additional calcium supplementation may be necessary.
- Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis, calcium monitoring is recommended.

In the setting of osteoporosis, the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) trial is the largest single trial comparing denosumab with placebo for the prevention of fractures. In this study, there were no significant differences between the 3900 subjects who received denosumab and those who received placebo with regard to the total incidence of adverse events, serious adverse events, or discontinuation of study treatment because of adverse events, no increase in the risk of cancer or overall rate of infection, cardiovascular disease, delayed fracture healing, or hypocalcaemia, and there were no cases of ONJ (11).

Because RANKL is expressed on subsets of T and B cells, there is a theoretical possibility that denosumab may be immunosuppressive. RANKL-deficient mice lack normal lymph node development and have inhibition of early T and B lymphocyte development (17). However, in clinical trials, a statistically significant or clinically meaningful effect on the immune system has not been observed. In one trial, denosumab therapy had no significant effect on mean white blood cell counts, absolute lymphocyte counts, T and B cell counts, or immunoglobulins, and no meaningful difference was seen regarding incidence of infection (10). Phase II and III trials of denosumab for the treatment and prevention of osteoporosis suggested a slight increase in the rate of certain infectious complications, including cellulitis (18). However, the overall infection rate did not differ from placebo, and an association between denosumab and serious adverse infectious events has not been observed in any of the three large Phase III registration trials in cancer patients.

Disease-specific use

There have been three international Phase III randomized, double-blind, active controlled studies including over 5700 patients comparing denosumab with zoledronic acid for the prevention of SREs in patients with breast cancer, prostate cancer, and other solid tumors or multiple myeloma with bone metastases which led to FDA approval of denosumab for this indication.

The three trials had identical study designs. Patients were randomly assigned to receive either denosumab 120mg Q4W administered as a subcutaneous injection or zoledronic acid 4mg (adjusted for creatinine clearance) administered intravenously Q4W and the corresponding placebos. Patients had histologically or cytologically confirmed tumors and radiographic evidence of at least one bone metastasis. Patients were ineligible if they had received bisphosphonate treatment for bone metastasis or had previous ONJ, unhealed dental or oral surgery, ECOG status more than two, or creatinine clearance less than 30 ml/ min. Supplementation with calcium and vitamin D was strongly recommended. All patients could continue to receive anticancer therapies. The primary endpoint was time to first SREs, with the study powered to detect noninferiority of denosumab versus zoledronic acid. Secondary endpoints included time to first on-study SRE (superiority test) and time to first and subsequent on-study SRE (multiple event analysis).

**Breast cancer**

In patients with breast cancer (n=2046), denosumab delayed the time to first on-study SRE by 18% compared with zoledronic acid (hazards ratio 0.82; 95% confidence interval 0.71–0.95; \(P = 0.001\) for noninferiority, \(P = 0.01\) for superiority). Median time to first SRE was 26.4 months in the zoledronic acid group and had not been reached in the denosumab group at the time of the primary analysis. With an additional 4 months of blinded treatment, the median time to first skeletal-related event was reached in the denosumab arm at 32.4 months (19). Denosumab also reduced the risk of subsequent SREs by 23% (risk ratio 0.77; 95% CI 0.66–0.89, \(P = 0.001\)). Overall survival and disease progression were similar between the two groups.

Adverse effects (AEs) were different between the two arms, including the incidence of flu-like symptoms (acute-phase reactions, 27.3% with zoledronic acid versus 10.4% with denosumab) and renal toxicity (8.5% with zoledronic acid versus 4.9% with denosumab). No patient treated with denosumab and 10 patients (1%) treated with zoledronic acid experienced serious adverse events associated with acute-phase reactions during the first 3 days after treatment. These events included pyrexia (n = 7), bone pain (n = 2), and asthenia, back pain, chest pain, chills, headache, and malaise (n = 1 each). Nine of the 10 patients in the zoledronic acid group with serious acute-phase reactions required hospitalization or prolongation of hospitalization (20). AEs potentially associated with renal toxicity (8.5% v 4.9%; \(P = 0.001\)), especially severe (2.2% v 0.4%) and serious renal AEs (1.5% v 0.2%), occurred more frequently with zoledronic acid. The incidence of renal AEs among patients with baseline renal clearance ≤ 60 mL/ min was also higher in the zoledronic acid group (20.0%) than in the denosumab group (5.9%), and a greater proportion of patients had decreases in their baseline creatinine clearance from ≥ 60 mL/min to<60 mL/min with zoledronic acid (16.1%) compared with denosumab (12.7%). Expected decreases in serum calcium (which were generally mild and transient), phosphorus, and total alkaline phosphatase were observed in both groups. ONJ occurred infrequently (20 [2.0%] denosumab v 14 [1.4%] zoledronic acid) and the rates were not statistically significantly different between groups (\(P = 0.39\)).
cumulative incidence in the denosumab and zoledronic acid groups, respectively, was 0.8% and 0.5% at 1 year, 1.9% and 1.2% at 2 years, and 2.0% and 1.4% at 3 years. Known risk factors for ONJ, including history of dental extraction, poor oral hygiene, or use of dental appliance occurred in 18 (90%) of 20 and 10 (71%) of 14 patients in denosumab and zoledronic acid groups, respectively. Fifteen (75%) denosumab-treated and 11 (79%) zoledronic acid-treated patients who developed ONJ were receiving or had received chemotherapy, and four (29%) patients in the zoledronic acid group (v zero in the denosumab group) had received prior oral bisphosphonate therapy for osteoporosis. Antiangiogenic therapy has also been associated with an increased risk of ONJ. Four (20%) ONJ events in the denosumab group and two (14%) in the zoledronic acid group occurred in patients receiving antiangiogenic therapy. As of 10 (50%) denosumab-treated patients and six (43%) zoledronic acid–treated patients had resolution of the ONJ event; 10 (50%) denosumab-treated patients and nine (64%) zoledronic acid–treated patients reported local infection; and seven patients in each group had undergone limited surgical procedures such as debridement and sequestrectomy (21-23).

Patient-reported outcomes analyzed in the trial included pain using the Brief Pain Inventory and quality of life as assessed by the Functional Assessment of Cancer Therapy-General (FACT-G) score. 30 Patients were asked to complete the Brief Pain Inventory at baseline, day 8, and before each monthly visit through the end of the study. In patients with scores of no/mild pain at baseline (n=1042), median time to development of moderate/severe pain with denosumab was 295 days compared with 176 days in those treated with zoledronic acid (HR 0.78, 95% CI 0.67–0.92, P = 0.0024). Time to pain improvement was similar between treatment arms (median 82 days for denosumab, median 85 days for zoledronic acid; HR 1.02, 95% CI 0.91–1.15, P = 0.7245). Similarly, health-related quality of life was higher in the denosumab arm than in the zoledronic acid arm throughout the study as well as improvements in emotional and physical state (24).

Prostate cancer

The Phase III trial in prostate cancer randomized 1904 patients with metastatic castrate-resistant prostate cancer to either denosumab or zoledronic acid treatment using an identical double-blind, active-controlled design. Patients with bone metastases from prostate cancer and high urinary NTx levels have an increased risk of SREs, time to a first SRE, disease progression, and death (25, 26).

Denosumab delayed the time to a first SRE by 18% (a median of 3.6 months) compared with zoledronic acid (hazard ratio=0.82, 95% CI, 0.71–0.95; P=0.0002 for noninferiority and P=0.008 for superiority). Also it delayed the time to multiple SREs, reducing the risk by 18% (rate ratio=0.82, 95% CI, 0.71–0.94, P=0.008). Overall survival, disease progression and median prostate-specific antigen levels were similar between the treatment groups throughout the study. At week 13, the decrease in urinary NTx/creatinine was significantly greater in the denosumab group (median decrease of 84% in the denosumab group vs 69% in the zoledronic acid group, P = 0.0001). Overall, occurrences of AEs were similar between the groups. Hypocalcaemia was more common in the denosumab group with no fetal episodes (13% in the denosumab group versus 6% in the zoledronic acid group, P = 0.0001). The cumulative rate of ONJ between the two groups was not statistically significant, occurring in 1% (12 patients) in the zoledronic acid group versus 2% (22 patients) in the denosumab group. AEs associated with acute-phase reactions occurred in 8% of patients on denosumab and 18% of patients on zoledronic acid. Adverse events related to renal impairment were similar between the two groups, at 15% in the denosumab group and 16% in the zoledronic acid group. However, the zoledronic acid group required more frequent dose adjustment / holding for renal dysfunction.

Solid tumors other than breast and prostate cancer

The third Phase III trial of denosumab in the setting of metastatic disease was carried out in 1776 patients with multiple myeloma or solid tumors other than breast or prostate cancer with at least one bone metastasis or osteolytic lesion. The design was identical to that of the other two Phase III trials described previously. Approximately 40% of enrolled patients had non-small cell lung cancer and 10% had multiple myeloma. Only 20% of patients remained on study, with the majority of patients discontinuing therapy as a result of death (35%), withdrawal of consent (15%), or disease progression (13%). This trial had the shortest median time on study at approximately 7 months in both treatment groups (27).

The median time to first on-study SRE was 20.6 months for denosumab and 16.3 months for zoledronic acid. Denosumab was noninferior to zoledronic acid in delaying time to first on-study SRE (HR 0.84, 95% CI 0.71–0.98, P = 0.0007), with superiority for denosumab nearing statistical significance at a P value of 0.06. Also denosumab failed to reduce time to first and subsequent SREs significantly with an HR of 0.90 for denosumab compared with zoledronic acid (95% CI 0.77–1.04, P = 0.14). Overall survival and disease progression were similar between the groups. The smaller number of patients randomized and shorter time on study yielded fewer SREs in this trial compared with the similarly designed breast and prostate trials, and thus may be the reason for the less dramatic improvements with denosumab seen in this study.

Denosumab resulted in greater suppression of the urinary NTx/creatinine ratio (76% decreases in the denosumab groups versus 65% in those on zoledronic acid, P= 0.001). When stratified by tumor type, the HR for time to first on-study SRE for denosumab versus zoledronic acid was 0.84 (95% CI 0.64–1.10, P = 0.20) for non-small cell lung cancer and 0.76 for other solid tumors (95% CI 0.62–0.99, P= 0.04). However, the HR for the 180 patients treated with multiple myeloma was only 1.03 (95% CI 0.68–1.57, P = 0.89) and thus the FDA approval of denosumab is limited to patients with solid tumors and excludes treatment of patients with multiple myeloma. Pain control was monitored at baseline, day 8, and before each monthly visit by the Brief Pain Inventory. Patients on denosumab experienced a delay in clinically significant pain worsening compared with patients on zoledronic acid (HR 0.85, 95% CI 0.73–0.98, P = 0.02), with the similar rates of overall adverse events (28, 29). Hypocalcaemia occurred more frequently in the denosumab group as compared with the zoledronic acid group (10.8% versus 5.8%, including grade 3 or 4 hypocalcaemia in 20 patients (2.3%) on denosumab and nine patients (1.0%) on zoledronic acid. The rates of ONJ were similar between the two groups (11 patients (1.3%) in the zoledronic acid group versus 10 patients (1.1%) in the denosumab group) and were seen primarily in patients with known risk factors. Acute-phase reactions were more common in the zoledronic acid group (14.4% zoledronic acid versus 6.9% denosumab). Dose reduction was required in 17.3%, and 8.9% of doses were held in patients on zoledronic acid due to renal dysfunction. Despite these dose adjustments, renal dysfunction was more common in the zoledronic acid group (10.9% versus 8.3%).

The effects of denosumab versus zoledronic acid were evaluated with respect to time to first on-study SRE for noninferiority (primary endpoint) and superiority (secondary endpoint), and time to first and subsequent SRE (secondary endpoint). A total of 5723 patients were evaluated, 2861 in the zoledronic acid group and 2862 in the denosumab group. In this combined analysis,
denosumab significantly prevented or delayed the time to first on-study SRE or hypercalcaemia of malignancy, with a risk reduction of 17% (HR 0.83, 95% CI 0.76–0.90, P = 0.001 for both noninferiority and superiority). The median time to first on-study SRE was 27.7 months with denosumab versus 19.4 months with zoledronic acid, resulting in a median delay of 8.2 months in favor of denosumab therapy. The effect of denosumab was consistent across all types of SREs (fracture, radiation, surgery, and spinal cord compression) (30, 31). These data are summarized in table 1.

Table 1: Hazard ratios for development of SREs by type.

<table>
<thead>
<tr>
<th>Type of SREs</th>
<th>Hazard ratio(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SREs</td>
<td>0.83 (0.76–0.90), P= 0.001 in favor of denosumab</td>
</tr>
<tr>
<td>Pathological fracture</td>
<td>0.86 (0.76–0.96), P= 0.090 in favor of denosumab</td>
</tr>
<tr>
<td>Radiation to bone</td>
<td>0.77 (0.69–0.87), P= 0.001 in favor of denosumab</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>0.89 (0.65–1.21), P = 0.45 in favor of denosumab</td>
</tr>
<tr>
<td>Surgery to bone</td>
<td>0.86 (0.61–1.21), P = 0.38 in favor of denosumab</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>0.63 (0.41–0.98), P = 0.042 in favor of denosumab</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; SRE, skeletal-related events.

In addition, combined analysis from the Phase III trials in patients with metastatic breast cancer and in patients with solid tumors other than breast or prostate cancer showed a significant decrease in hypercalcaemia of malignancy in those treated with denosumab (HR 0.63, 95% CI 0.41–0.98, P = 0.042) (32), with similarity between two groups as regard; disease progression, overall survival and the incidence of all AEs. However, as with the individual trials, there was an increased incidence of hypercalcaemia in the denosumab group (9.6% versus 5.0%) and acute-phase reactions (20.2% versus 8.7%) in the zoledronic acid group (table 2).

Table 2: summarizes the adverse events observed in the three Phase III trials in patients with breast cancer, prostate cancer, and other solid tumors or multiple myeloma.

<table>
<thead>
<tr>
<th>Adverse event of interest</th>
<th>Denosumab (n=2841)a</th>
<th>Zoledronic acid (n=2841)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event (total)</td>
<td>2734(96.2%)</td>
<td>2745(96.8%)</td>
</tr>
<tr>
<td>Adverse event leading to study discontinuation</td>
<td>270 (9.5%)</td>
<td>280 (9.9%)</td>
</tr>
<tr>
<td>CTCACE grade 3 or more</td>
<td>2000(70.4%)</td>
<td>2009(70.8%)</td>
</tr>
</tbody>
</table>

Note: a Patients who received at least one dose of active drug.

Conflicts of interest: The authors certify that is no potential or actual conflict of interest related to this article.

Future uses

The role of denosumab for the prevention of SREs in patients with bone metastasis from solid tumors has now been established in three large, well-designed, and definitive trials. Potential clinical questions include indications for and timing of transition from intravenous bisphosphonate to denosumab. Obvious indications for switching to denosumab include progressive renal insufficiency or intolerance to side effects associated with bisphosphonates. The Phase III STAND (Study of Transitioning from AleNdronate to Denosumab) trial looked at sequential use of oral bisphosphonates followed by denosumab in postmenopausal women with primary osteoporosis (34). Postmenopausal women at least 55 years of age with lumbar spine or total hip bone mineral density measurements corresponding to a T score of -2.0 to -4.0 who had been receiving alendronate at 70 mg/week for at least 6 months were eligible. Subjects were randomized to denosumab 60 mg subcutaneously every 6 months versus continuing oral alendronate. All subjects were supplied with calcium and vitamin D supplements daily.

The primary efficacy endpoint was the percentage change in total hip bone mineral density after 12 months of therapy. Bone mineral density at the total hip increased significantly more in patients transitioned to denosumab (1.90%, 95% CI 1.61%–2.18%) compared with patients continuing on alendronate (1.05%, 95% CI 0.76%–1.34%), (P = 0.0001). Sequential use has also been explored in a Phase II trial in which 111 patients with solid tumors and bone metastasis previously treated with bisphosphonate were randomized to continue intravenous bisphosphonates versus switching to subcutaneous denosumab 180 mg subcutaneously every 4 or 12 weeks (35). Urinary NTx was reduced to below 50 nmol/L by week 13 (the primary endpoint) in 71% of patients on denosumab versus 29% of patients who continued on intravenous bisphosphonates (P = 0.001). The percentage of patients experiencing a first on-study SRE during the 25-week treatment period was 8% in the denosumab arm versus 17% in the intravenous bisphosphonate arm (odds ratio 0.31; 95% CI 0.08–1.18). These trials suggest a role for switching to denosumab in patients who are currently receiving oral or intravenous bisphosphonates and experience a skeletal-related event or who continue to have an elevated urinary NTx level despite bisphosphonate therapy. There are currently no data to support the combined use of a bisphosphonate plus denosumab to reduce osteoclast activity further due to the risk of increased toxicity especially ONJ and hypercalcaemia.

Several trials in early-stage breast cancer patients suggest a role for bone-modifying agents in improving disease-free survival. The ABCSG-12 trial in premenopausal women with early-stage breast cancer is suggesting a role for bone-targeted therapy in the prevention of breast cancer recurrence (36). Unfortunately, the subsequent AZURE (Adjuvant Zoledronic Acid to Reduce Recurrence) trial, failed to show a similar improvement in breast cancer recurrence (37). However, in subgroup analysis, there was an improvement in both disease-free and overall survival in older women treated with zoledronic acid. There are data to suggest that RANKL may also be integral to the spread and propagation of cancer cells in bone (38). The Phase III D-CARE trial is underway to assess the effect of denosumab on disease recurrence in patients with stage II and III high-risk, early-stage breast cancer (39).

The full results the D-CARE trial will help define the role of denosumab therapy or who remained on denosumab therapy for up to 5 years (33). In this analysis of patients from the open-label extension phase of the metastatic breast cancer registration trial, no new safety signals were observed in patients who switched from zoledronic acid to denosumab therapy or who remained on denosumab therapy for up to 5 years (median time on denosumab 19.1 months, range 0.1–59.8 months).

Note: a Patients who received at least one dose of active drug. Abbreviation: CTCACE, Common Terminology Criteria for Adverse Events.
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Small Cell Esophageal Carcinoma; A rare diagnosis, Cases reports and review of the literature

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Definition

Primary small cell carcinoma (SCC) of the esophagus is a relatively rare malignancy, accounting for 0.05 – 4% of all esophageal malignancies. It is a highly aggressive tumor associated with a poor prognosis, similar to SCC that arises in the lung and other extra pulmonary organs, including breast, ovary, uterine cervix, liver, salivary gland, stomach, colon, prostate, urinary bladder, and kidney. Histologically, SCC is characterized by neuroendocrine-like architectural patterns, including nested and trabecular growth with common features including peripheral palisading and rosette formation in the tumors. Some SCC cases include carcinomas such as squamous cell carcinoma and adenocarcinoma (approx. 90–95% of all esophageal cancer worldwide) and adenocarcinoma (approx. 50–80% of all esophageal cancer in the United States)\(^1\)

A general rule of thumb is that a cancer in the upper two-thirds is a squamous cell carcinoma and one in the lower one-third is an adenocarcinoma\(^2\)

Primary small cell esophageal carcinoma (SCEC) is a rare and aggressive disease for which there is no recommended standard treatment at this time.

Prevalence and risk factors

Cancers arising from the esophagus and gastro esophageal junction are relatively uncommon in the United States; there were approximately 38780 new cases and 25610 deaths in 2012\(^2\). Worldwide, however, esophageal cancer is the eighth most common malignancy and the sixth most common cause of cancer-related death\(^3\). The epidemiology of esophageal cancer has changed dramatically during the latter half of the 20th century. Although 40 years ago SCC accounted for more than 90% of all esophageal tumors in the United States, diagnoses of esophageal AC have significantly increased and is becoming endemic, especially in developing world. However, SCC remains the most common worldwide. The mean age at diagnosis is 67 years, and men are affected more frequently than women, particularly among patients with AC.

Tobacco and alcohol are major risk factors for esophageal cancers. Obesity and high body mass index are also strong risk factors. Significant changes have been observed in histology and location of upper GI tumor in UA as well as in Europe. Small cell carcinoma was first described by McKeown in 1952. Histologically it is not different from lung small cell cancer. They both originate from Kulchitsky”s or amine precursor uptake and decarboxylation cells of neuroectodermal origin.

The staging of small cell esophageal is similar to small cell carcinoma of lung staging. Small cell carcinoma of esophagus is a rare disease with poor prognosis and high rate of metastases. In small cell carcinoma patients present with extensive metastasis to the liver, adrenal gland, lymph nodes, and other organs\(^4-5\)

Osugi et al. reported that the overall survival after esophagectomy was significantly lower in patients with Small cell carcinoma as compare to squamous cell carcinoma\(^5\)

For definitive diagnosis of this tumor, biopsy is necessary, although exact biopsy of the tumor is difficult because the tumor surface is covered with normal epithelium. Mitani et al reported that the tumor was confined to the sub mucosal layer in all long-term survivors\(^6\)

In some cases, it is sometimes impossible to diagnose the tumor by means of endoscopy or endoscopic biopsy. For this reason, PET-CT seems to be very useful. Because esophageal cancer often spreads to the lymph nodes or other adjacent organs, CT imaging has been commonly used to diagnose the presence of metastases. The advantage of FDG-PET is that it can be used to diagnose the original lesion and the presence of metastases in the lymph nodes and adjacent organs. Regarding the use of FDG-PET in the diagnosis of esophageal cancer; Yeung et al. compared FDG to CT in the detection of primary lesions in 109 patients with esophageal cancer. They reported that sensitivity was 80% for PET and 68% for CT, specificity was 95% for PET and 81% for CT, and accuracy was 86% for PET and 73% for CT\(^7\)

Case No. 1

59 years old male, with Diabetic Mellitus, Hypertension, hepatitis C positive, and CVA in 2008 presented in December 2011 with a 2 months history of dysphagia to solid foods, loss of appetite and weight loss of about 10 kilograms. Physical examination at the time was otherwise completely unremarkable. There were no palpable lymph nodes. Upon first visit in Tawam Hospital several investigations were done including Endoscopy (EGD) which showed ulcerated polypoidal lesion that started from 32 cm and extending up to 41cm of esophagus and erosive duodenitis, a biopsy...
taken showed Tumor cells expressing CK, EMA, Synaptophysin, chromogranin and TTF-1 strongly;Mib labeling index is 30 to 40% The Ki-67 index is 80%. Positive Stain for Helicobacter pylori is. The features were consistent with Small cell carcinoma. All blood workup including tumor markers were within normal limits. A CT scan chest/Abdomen showed; a circumferential mass lesion in the distal 9 to 10 cm of esophagus up to the GE junction.with Three large paraesophageal lymph nodes adherent to the esophageal mass with the largest one measuring 4.6 to 5.1cm; The mass partially encased the celiac axis origin.

He was started on first line chemotherapy with Cisplatin 50 mg/m² with Etoposide (VP-16) 180 mg/m² with all supportive treatment. And has completed 6 cycles after which he a CT scan done showed almost total resolution of lower esophageal wall thickening with Regression in size of the lesser sac mass with No sign of distant metastasis.

He was followed up until September 2012 when a repeat CT scan showed progressive disease with bone metastases; MRI of the spine was done showing soft tissue mass with pressure effect on the epidura and nerve root so he received radiotherapy to spine T2-T7 20 Gy and 4 fraction; he was also started on Topotecan as 2nd line with Zometa after 2 cycles of chemotherapy he developed a stroke and duplex scan of carotid artery showed complete occlusion of the right internal carotid artery (history of CVA) he was switched to FOLFIRI; he completed one cycle and developed febrile neutropenia and severe mucositis; his condition kept worsening until his family decided to stop all treatment and take him back to his home country as January 2013

Case No. 2

57 years male heavy smoker; history of Diabetic Mellitus, Hypertension and Dyslipidemia; underwent a coronary artery bypass graft surgery (CABG) in 2006 Patient first presented to Taiwan Hospital in June 2010 with persistent dysphagia and vomiting for 3 months duration and a significant weight loss. Physical examination was otherwise completely unremarkable, no palpable lymph nodes. EGD showed thickening of the lower esophageal wall, Mild stenotic polypoid lesion starting at 28 cm from the incisors, in the lower esophagus Barrett mucosa

He was started on first line chemotherapy with Cisplatin 50 mg/m² with Etoposide (VP-16) 180 mg/m² with all supportive treatment. And has completed 6 cycles after which he a CT scan done showed almost total resolution of lower esophageal wall thickening with Regression in size of the lesser sac mass with No sign of distant metastasis.

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In Extended disease cases, it should be treated with chemotherapy and/or radiotherapy.

Levenson et al and Kelsen et al recommended chemotherapy as first line treatment. Beyer et al reported as combination chemotherapy is the best choice. Recently he also reported about limited disease treated by adjuvant therapies with surgical resection and achieved longer survival time they also mentioned that patient who received preoperative chemotherapy survived 33 months.

Radiotherapy is as effective as in small cell lung cancer in limited disease, but only for local control, radiation alone if not first line choice. Cisplatin is reported as better treatment for small cell of esophagus. Tanabe et al reported that five drugs (CDDP, VP-16, VCR, ADM, CPA), CDDP and VP-16 are the best choice and more effective and WBRT should be applied as prophylactic treatment. They also reported patient treated with chemotherapy also died from Meta brain disease. Since pathology of both small cell carcinoma of lung and esophagus is same they both treated with same chemotherapy regimen. However, extensive metastasis to the liver, adrenal gland, lymph nodes, and other organs, is often seen at the time of diagnosis.

In summary, small cell carcinoma of esophagus is almost impossible to get complete heal, local treatment like operation and radiotherapy are not good options alone, it should be treated with multi drug regimen chemotherapy with CDDP, with or without radiotherapy as first line.

Discussion

Small Cell carcinoma of the esophagus is very rare and it represents about 1-2% of all esophageal cancers. McKeown first described two cases after autopsy as esophageal small cell carcinoma as oat cell carcinoma in 1952. It cannot be treated adequately only by esophagectomy, although it recommended only for limited cases, in many cases the metastases were found during operation.

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6. Esophageal Cancer; Ahmed Absi; David J. Adelstein; Thomas Rice


Metastatic Triple-Negative Breast Cancer; Unusual Presentation

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Abstract

Triple-negative breast cancer (TNBC) which does not over-express HER-2 (human epidermal growth factor receptor 2), estrogen receptor, or progesterone receptor creates the biggest challenge in the treatment of metastatic breast disease. Patients diagnosed with TNBC have shown an inferior prognosis with the increased likelihood of distant recurrence including brain metastases within five years of diagnosis. We present an interesting case of a 37-year-old female diagnosed with invasive high-grade triple-negative breast cancer, who presented with right breast mass and multiple cervical and axillary LNs. Restaging work up document no visceral metastasis. She was treated was multiple lines of chemotherapy with complete response (CR), but unfortunately with rapid relapse after each one. The unusual is that all relapses were in cervical area only without any visceral involvement or local recurrences which resembles lymphomas or head and neck tumors.

Introduction

Breast Cancer (BC) is by far the most frequent Cancer of women worldwide. The American Cancer Society estimates that 234,580 Americans will be diagnosed with breast cancer and 40,030 will die of the disease in the United States in 2013[1]. BC is second only to lung cancer as a cause of cancer death and its incidence has increased steadily over the past few decades but the mortality appears to be declining, suggesting a benefit from early detection and more effective treatment [2, 3]. Among Saudi patients, there is a significant increase in the incidence of breast cancer, which occurs at an earlier age than in western countries [4].

Due to advances both in early detection and in adjuvant treatment, mortality rates from breast cancer have been decreasing steadily in most countries since the early 1990s. However, it is still the leading cause of cancer mortality in women. Approximately 4–6% of breast cancers are metastatic at diagnosis; of those approximately one-fifth will survive 5 years. Depending on prognostic factors, in the worst-case scenario, up to 30% of node-negative and up to 70% of node-positive breast cancers will relapse. The prevalence of metastatic disease is high because many women live with the disease for several years [5]. Triple negative breast cancers (TNBC), defined by the lack of estrogen receptor (ER), progestosterone receptor (PR) and epidermal growth factor receptor 2 (Her2/ cerbB2/ EGFR2) expression, account for 10 to 20% of all breast carcinomas in Asian and Western populations, but occur at much higher frequencies in individuals of African descent. These tumors are usually of higher histological grade (Grade 3) and are associated with distinctive metastatic patterns, shorter time to recurrence and earlier mortality [6].

TNBC is highly proliferative and sensitive to systemic chemo-therapies. However, despite its relative sensitivity to chemotherapy, patients outcome are poor compared with other subtypes of breast cancer (HER2+ or ER+). The cause of death of patients with TNBC is often recurrence (30–40% of TNBC cases), which presents as distant metastasis.

Case report

37 years old female patient started to complain about one year ago from right axillary painless mass that appeared gradually and increased in size progressively, but she ignored to seek medical advice, nine months later there were two new masses; one in right breast and the other in right cervical region, at that time she attended to her local hospital where biopsy was taken and revealed invasive duct carcinoma grade III, triple negative with high ki 67. Biopsy from right cervical mass showed metastasis from breast origin, but unfortunately she lost follow up. 6 weeks later the patient had extreme edema of the right upper limb, enlarged right breast with diffuse swelling of right upper limb. At that time, the patient was transferred to our center (King Abdullah Medical City) for further work up. On examination the patient had performance status 1 according to ECOG, the whole right breast was edematous, tender, enlarged, hot with upper outer quadrant mass 3 x 5 cm with nipple retraction and peau d’ orange. Hard fixed right axillary mass about 2 x 3 cm, right hard fixed cervical mass 5x4cm with extreme edema of the right upper limb, multiple scattered left cervical lymph nodes the largest 2x2cm . The contra lateral left axillary lymph node (LN) 1x2 cm, with no other finding. She was a premenopausal with gynecological histories of 3 pregnancies; the first when she was 18 years old, and no history of
abortion was noted. She had positive family history of cancer as her mother had lymphoma. She denied the use of an oral contraceptive pills.

Slide review showed the same pathology and the same phenotype (figure 1a, b, c, d). Staging work up was done in form MRI of breasts, CT chest, abdomen, pelvis; brain and bone scan with no evidence of visceral metastatic. Doppler U/S of right upper limb revealed DVT of subclavian, axillary and proximal brachial vein. Laboratory investigations were in normal ranges, with CA15.3 = 25 u/ml. The patient was diagnosed as stage IV (T4a N2 M1); and started chemotherapy in the form of paclitaxel / carboplatin (paclitaxel 175 mg/m^2 / carboplatin AUC=5) with therapeutic dose of enoxaparin. At the time of the second cycle; the right breast showed decrease in size with no palpable LN in the right axilla, multiple right cervical LNs the largest was 1 cm in size, the right upper limb swelling improved with no hotness or tenderness, normal left breast and left axillary hard mobile LN 1x1.5 cm. CBC showed neutropenia with TLC 3.6, ANC 0.8, where second cycle of chemotherapy was postponed. After one week CBC recovered and the second cycle was given and continued for total four cycles with G-CSF support. Re-evaluation by C T chest & Doppler U/S after the fourth cycle of chemotherapy showed only skin thickening, edema of the right breast with disappearance of the previously reported right outer aspect breast mass, with regression of the right axillary LN 1.5x1 cm (previously 3.4x2 cm), regression of the bilateral cervical LN largest was 1.3x0.8 cm, with patent right jugular, subclavian, axillary and brachial veins. Then the patient completed 8 cycles of chemotherapy and started follow up. Two months post the eighth cycle, the patient presented to ER with fever and right submandibular hard fixed swelling (4.76x2.05 cm), FNA was taken that revealed metastatic cancer most likely of breast origin, CT head, neck, chest, abdomen and pelvis was done revealed multiple enlarged right submandibular LNs (figure 3) with features suggestive of infection with no other findings suggestive of metastasis. True-cut biopsy was taken from the mass revealed metastatic adenocarcinoma of breast origin with negative ER, PR, HER-2/neu, CT brain was done with no evidence of metastasis (figure 2a, 2b).
Second line chemotherapy AC (Adriamycin 60 mg/m²– cyclophosphamide 600mg/m²) was started, patient received two cycles with delay between them caused by neutropenia, at the time of the third cycle clinical examination revealed regression of the right submandibular mass to 1x1cm, and this mass disappeared after the third cycle. Patient received the fourth cycle with 25% reduction because of the neutropenia post chemotherapy. Re-evaluation (Figure 4) was done with CT neck, chest, abdomen, pelvis and bilateral mammography showed only thickening of the right breast skin.

Then due to bone marrow exhaustion from repeated chemotherapy and poor tolerance even with G-CSF support, we shifted to capecitabine, which is FDA- approved for such condition and recommended for TNBC [7]. Capecitabine was started and continued for 6 cycles, re-evaluation was done by CT neck, chest, abdomen & pelvis showed progressive enlargement of cervical LNs bilaterally with largest 2.8x2.2cm in left upper deep cervical LN. Figure 5

Chemotherapy was changed to weekly paclitaxel 80 mg/m ² as a fourth line, patient received 6 weeks of weekly paclitaxel. Re-evaluation with CT neck, chest, abdomen & pelvis there was significant reduction in the size of the previously noted bilateral deep cervical lymph nodes, largest on left side measures 1.19 x 0.84 cm with no evidence of other metastasis. Figure 6

Discussion

TNBC is defined by the absence of ER, PR, and HER-2 Over expression. It accounts for 15–20% of all breast cancer cases [8, 9], and occurs at a higher frequency in young premenopausal women with African Ancestry (AA) [10]. High body mass index (BMI) and high parity, instead of low parity in other types of breast cancer, have been associated with increased risk for TNBC [11–13]. TNBC is associated with an overall poor prognosis as exemplified by a higher rate of early recurrence and distant metastasis to brain and lungs compared to other breast cancer subtypes [14, 15]. The unfavorable clinical outcome is partly explained by its aggressive pathologic features including a higher histology grade and mitotic index [16].

Chemotherapy is the only systemic therapy currently available for TNBC and is curative in a subset of patients with chemotherapy-sensitive disease. A higher rate of pathologic complete response (pCR) to standard chemotherapy has been observed in patients with TNBC compared to ER+ disease. A pCR rate of 22% in TNBC versus 11% in ER+ disease was reported in a study of over 1 000 patients treated with neoadjuvant anthracycline and taxane based chemotherapy regimens [17]. The excellent outcome associated with the pCR, however, is in contrast to the high risk of recurrence and cancer-related deaths in those with residue disease. Although alternative agents such as platinum compounds have demonstrated promising activity, up to 70–80% of patients have residual cancer following neoadjuvant cisplatin [18]. In the metastatic setting, TNBC is typically associated with an initially higher response rate, but in a shorter time to progression following treatment with existing chemotherapy agents, resulting a shorter overall survival compared to ER+ breast cancer in multiple studies [19]. The underlying molecular mechanism for this paradox is yet to be elucidated, although one could hypothesize that the inherent genomic instability of TNBC renders the possibility of a faster adaptation to the cytotoxic effect of chemotherapy.

Our patient was diagnosed as stage IV and started on chemotherapy; paclitaxel /carboplatin, she received 8 cycles with good response after 4 cycles and complete response after 8 cycles with recanalization of all thrombotic veins but unfortunately after two months, she relapsed by submandibular lymph nodes which proved to be metastatic from breast origin with the same pathology and the same phenotype. We started AC protocol with complete response after 4 cycles but due to exhaustion of bone marrow and neutropenic fever after third cycle, the fourth cycle was with 25 % reduction and then she was shifted to capcitabine but after 6 cycles there was disease progression, at this time she was shifted to weekly paclitaxel with CR after 6 weeks.
As usual Triple-negative breast cancer is highly proliferative and sensitive to systemic chemo-therapies. However, despite its relative sensitivity to chemotherapy, patient outcomes are poor. This means that chemosensitivity of TNBC does not reflect whether the cancer will metastasize. Therefore, the mechanism of metastasis needs to be studied separately from that of tumorigenicity. But the unusual in this case is the presentation and in the multiple relapse in non visceral organs; all in cervical and submandibular lymph nodes.

The treatment options for chemotherapy-resistant TNBC are limited. The established targeted therapies, including endocrine treatment and HER2-targeted agents, are ineffective. Although several small molecule inhibitors and monoclonal antibodies against important cellular pathways have been tested in clinical trials, none has entered clinical practice due to limited efficacy. A better understanding of the underlying biology of TNBC is therefore needed to identify new therapeutic targets and to pinpoint which TNBC patients may benefit from them. Recent advances in microarrays and DNA sequencing technologies have made it possible to analyze the tumor at the genomic level. Such comprehensive analysis at the genomic, epigenomic, and proteomic levels and follow-up, Ann Oncol (2011) 22 (suppl 6): vi25-vi30

Conclusion

TNBC is a heterogeneous disease with different types depends on molecular classification, so molecular diagnostic methods appear to be more important for selection of potential prospective patients with triple negative breast cancers who may benefit from many target therapy. Chemotherapy-resistant triple negative breast cancer remains a major cause of mortality and currently lacks any proven targeted therapy.

The development of “genome-first approaches” where patients are stratified upfront and prospectively placed into clinical trials designed to address the therapeutic hypotheses generated by analysis of individual tumor profiles is surely the most logical approach to consider.

Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest: The authors certify that is no potential or actual conflict of interest related to this article.

References

Case Report


News From The Arab World

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Dear Colleague

It is a great pleasure and privilege to welcome you to attend 2nd Conference of palliative care under the auspices of The Ministry of Health on 13th – 15th of April 2014 in Kuwait.

The purpose of this 3-days conference is to provide a forum for update information on a broad range of topics covering palliative medicine, its therapies, current guidelines and clinical research, as well as fundamental background studies. This international conference will be attended by physicians, pharmacists, nurses, psychologists, social workers, dietitian, physiotherapist, other healthcare professionals and interested parties from all over Kuwait and other countries.

This conference will enable the exchange of ideas and knowledge between the different disciplines for facilitating research and clinical interdisciplinary collaborations focusing on palliative management.
Vision

Our vision is to institutionalize palliative medicine in the management of patients with progressive life-limiting conditions such as advanced malignancy, to correct and improve public perception of the importance of integrating palliative care in the management of the aged, sick and hopeless patients to alleviate their symptoms and decrease their sufferings and to improve their quality of life.

Objectives

1. Palliative care models.
2. Updates in pain management.
4. Psychosocial and communication issues in palliative care.
5. Role of physiotherapy and nutrition.
6. Debates in palliative care management.

Abstract Submission

Interested participants are encouraged to prepare their abstracts and submit their papers and researches on any topic relating to the objectives of this conference. Deadline for abstract submission is 31st of January 2014 midnight by GMT.

Language of the Conference

English

Registration Fees

Early bird
Before 31st January 2014
5 K.D

Late bird
After 31st January 2014
10 K.D

Visas

The organizing committee will arrange for the visas of participants and invited speakers. Copies of the main pages of the passport should be sent not later than 15 February 2014. Passports should be valid at least 6 months from the start of the conference.

Travel and Accommodation

The Organization Committee will cover the costs of travel and accommodation of invited speakers. Participants outside the State of Kuwait should shoulder their own travel and accommodation expenses.

We look forward to see you in Kuwait.

Dr. Khalid El Saleh
Consultant of Radiation Oncology
Head of the Palliative Care Team

For more information, visit our website: www.pcckw.com or Contact: Dr. Zakeer Ali Khan, (Secretary)
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## Cancer Awareness Calendar

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<td>FEBRUARY</td>
<td>Screening and Early Detection Awareness Month</td>
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Objectives & Scope Of The PAJO

The Pan Arab Journal of Oncology (PAJO) is the official Journal of the Arab Medical Association Against Cancer (AMAAC). It is a quarterly publication targeting health professionals interested in the oncology field. It is a multidisciplinary peer-reviewed journal that publishes articles addressing medical oncology, malignant hematology, surgery, radiotherapy, pediatric oncology, geriatric oncology, basic research and the comprehensive management of patients with malignant diseases in addition to international oncology activities, congresses & news.

The journal will be addressed, as a first step, mainly to the professionals in the hematology & oncology field in the Middle East region and North Africa. The goal is to share local & regional research activities news and to be updated with international activities. We hope, with your support, to achieve our following objectives:

1. Promote and encourage research activities in the Arab World.
2. Disseminate & analyze epidemiological local, regional and international data.
3. Update health professionals with the most recent advances, news & developments in the field of oncology.
4. Improve the level of scientific publications arising form the Arab World.
5. Keep health professionals connected and exposed to the activities of different Arab cancer societies.
6. Share with our immigrant compatriots their activities & feedback in this field.
7. Involve all health professionals interested in the field of Oncology within the multidisciplinary scope of the Journal.
8. Encourage post graduates students to submit their research work.

Instructions For The Authors

1. Manuscript Categories

1.1. Clinical trials
The Editor-in-Chief and an Associate Editor generally review Reports from clinical trials. Selected manuscripts are also reviewed by at least two external peer reviewers. Comments offered by reviewers are returned to the author(s) for consideration. Manuscript acceptance is based on many factors, including the importance of the research to the field of oncology & the quality of the study. Authors should focus on accuracy, clarity, and brevity in their presentation, and should avoid lengthy introductions, repetition of data from tables and figures in the text, and unfocused discussions. Extended patient demographic data should be included in a table, not listed within the text. Reports from Clinical trials are limited to 3,000 words of body text, excluding the abstract, references, figures, and tables. They are limited to six total figures and tables. All abstracts are strictly limited to 250 words. Titles are to be descriptive, but succinct. Results of clinical studies should be supported by a clear description of the study design, conduct, and analysis methods used to obtain the results. Reports of phase II & III studies should include from the protocol a clear definition of the primary end point, the hypothesized value of the primary end point that justified the planned sample size, and a discussion of possible weaknesses, such as comparison to historical controls. Phase I studies will be well received if they have interesting clinical responses, unusual toxicity that pointed to mechanism of action of the agents, and important or novel correlative laboratory studies associated with the trials.

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All reviews must be clinically oriented, ie, at least half the review must describe studies that detail human impact, marker effect on prognosis, or clinical trials. Review Articles should be prepared in accordance with the Journal’s Manuscript Preparation Guidelines, and will be reviewed in the same manner as Reports from Clinical Trials. Reviews are limited to 4,500 words of body text, excluding the abstract, references, figures, and tables. The editors also suggest a limit of 150 references.

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The Editor-in-Chief may solicit an Editorial to accompany an accepted manuscript. Authors who wish to submit unsolicited Comments and Controversies should contact the Editor-in-Chief, before submission to determine the appropriateness of the topic for publication in the Journal. Editorials should be no more than four to five pages in length.

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Articles about health economics (cost of disease, cost-effectiveness of drugs, etc) are highly encouraged.

1.5. Case Reports / Correspondence / Special Articles
Correspondence (letters to the Editor) may be in response to a published article, or a short, free-standing piece expressing an opinion, describing a unique case, or reporting an observation that would not qualify as an Original Report. If the Correspondence is in response to a published article, the Editor-in-Chief may choose to invite the article’s authors to write a Correspondence reply. Correspondence should be no longer than three pages in length. Special Articles present reports, news from international, regional societies as well as news from our compatriots.
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results and prognostic factors among 138 patients with advanced Hodgkin’s disease treated with the alternating MOPP/ABVD chemotherapy. Ann Oncol 5:S53-S57, 1994 (suppl 2)


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