ORIGINAL ARTICLE ◄

Concurrent chemoradiotherapy with docetaxel plus cisplatin (TP regimen) followed by consolidation chemotherapy with TP regimen in treatment of anaplastic thyroid cancer

Khaled N Abdel-Hakim, MD[1]

(1) The Department of Radiation Oncology & Nuclear Medicine, Ain Shams University

✉ *Corresponding Author: Dr Khaled Nagib Abdel-Hakim, MD*
Radiation Oncology, Nuclear Medicine Department, Ain Shams University, Cairo, Egypt
E-mail: hakimkn@hotmail.com

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Abstract

Purpose: To evaluate the efficacy and outcome of concomitant docetaxel/ cisplatin and limited field irradiation followed by consolidation docetaxel/ cisplatin in patients with anaplastic thyroid cancer (ATC).

Patients and Methods: This is a prospective phase II study that included 13 ATC patients. Eligible patients were treated first with surgical debulking of the tumor if possible, then by concomitant chemo-radiation with conventionally fractionated radiation (60 Gy in 2Gy fractions) to the gross or residual primary disease and regionally involved lymph nodes. This was followed by 4 cycles of consolidation chemotherapy /3 weeks.

Results: The median follow-up duration was 15 months (range from 6 to 30 months). The median survival was 16.8 months and the median progression free survival was 13.4 months. . After concomitant chemoradiation, 7 patients (53.8%) achieved objective response which improved to 69.2% at the end of treatment. A total of 7 patients (53.8%) had treatment failure, 3 patients (23%) had neck failure including 2 patients (15.3%) had exclusively neck failure, and 1 patient (7.6%) had neck and distant failure. Four patients (30.7%) developed distant metastasis. Neutropenia (23%), anemia (15.3%), nausea and vomiting (15.3%) and pharngo-esophagitis (7.6%) were the most severe, grade 3 and 4, acute toxicities recorded during concomitant chemoradiation. Neutropenia (30.7%) and anemia (23%) were the most pronounced, grade 3 and 4, toxicities during consolidation chemotherapy.

Conclusion: Concomitant chemo-radiation using TP regimen, with limited nodal irradiation followed by consolidation TP regimen improves the median overall and progression-free survival and response rate together with tolerable toxicity in ATC patients.

Introduction

Anaplastic thyroid carcinomas (ATC), in contrast to differentiated thyroid carcinomas, have a dismal prognosis (1-3). Most patients suffering from ATC die due to aggressive local tumour invasion causing suffocation (4,5). Although current therapy does not significantly improve survival rate, every effort should be made to control the primary tumour and thereby improve the quality of the remaining life. Surgery, radiotherapy, or chemotherapy used alone is seldom sufficient to control the disease (1, 6), while a combination of these modalities may improve local control (6, 7). The rationale for combining radio- and chemotherapy is that, as the toxicity of these modalities does not entirely overlap, an enhanced tumouricidal effect may be obtained (8).

Regarding the sequence of administration of radiation therapy and chemotherapy, induction chemotherapy (9) and alternating radiotherapy and chemotherapy (10) have been tried. Concurrent chemoradiotherapy has been reported to be a promising approach for improving the clinical outcomes. Among the chemotherapeutic agents, Doxorubicin and cisplatin have been established as effective agents for ATC, however, taxanes are recently attracting attention as promising antineoplastic drugs (11).

Docetaxel is a representative of taxanes which acts by binding to cellular *b*-tubulin, increasing its polymerization and promoting microtubule assembly. Because this drug–tubulin binding inhibits tubulin depolymerization, the cells become arrested in the M-phase of the cell cycle (12). Induction of mitotic arrest by these agents served as the rationale for exploring taxanes as possible radiosensitizing agents (13). In addition to mitotic arrest, docetaxel possibly also exerts cytotoxicity on radioresistant S-phase cells via another cell cycle mechanism (14). Docetaxel has been reported as an effective anticancer agent against ATC. Disease control rates of 43% have been reported following therapy with docetaxel as a single agent in patients with locally advanced ATC (15).

Regarding the effects of combined docetaxel and radiation therapy, Troch et al. conducted a Phase I study on cases locally advanced ATC, and concluded that therapy with docetaxel administered concurrently with conventional radiotherapy is a feasible and effective treatment method for unresectable ATC (16). However, reports of concurrent chemoradiotherapy using docetaxel-based chemotherapy are still scarce. Under these circumstances, we conducted a study of concurrent docetaxel-cisplatin and radiation therapy followed by consoliation docetaxel- cisplatin for ATC patients whose clinical outcomes were not expected to be satisfactory with either modality alone. The purpose of this study was to evaluate the response rate and preliminary clinical outcomes of this approach. In addition, the incidence of toxicity in order to evaluate feasibility was also analysed.

Patients and Methods

This trial was conducted on 13 pathologically confirmed ATC patients who presented to the Radiation Oncology Department Ain Shams University hospitals between May 2008 and August 2010. Patients older than 20 years but not more than 75 years were eligible for this study if they had at least one measurable lesion that could be assessed according to the response evaluation criteria in solid tumors (RECIST), performance status (PS) of 0-2 according to the Eastern Co-operative Oncology Group (ECOG), adequate hematologic status (leukocyte count >4000/uL, absolute neutrophil count (ANC) ³1500/uL, platelets ³100,000/uL and hemoglobin ³10g/dl), adequate kidney function (creatinine clearance (CrCl) ³60mL/min and serum creatinine level of 1.5mg/dl) and adequate liver functions (bilirubin <2mg/dl, and transaminases levels < three times the upper normal limit). Exclusion criteria included prior malignancy, prior chemotherapy or radiotherapy to the neck or concurrent serious medical illness. All patients were required to provide written informed consent before joining the study, and the protocol was approved by the institutional ethics committee.

Surgery

When feasible, patients were first operated. Aggressive surgical procedures were not possible due to adherence of the tumors to vital structures (pharynx, esophagus, larynx, trachea, or recurrent laryngeal nerve). Maximal debulking of all resectable gross tumor was performed to control local symptoms of neck mass or impending tracheal obstruction, independently of the presence or absence of distant metastases.

Concomitant chemoradiation

Chemotherapy and radiotherapy began simultaneously. Docetaxel and Cisplatin were given intravenously in a dose of 20 mg/m2/day on days 1, 8, 15, 22, 29 and 36. The chemotherapy was given at approximately 30-60 minutes before receiving radiotherapy. Complete blood picture with differential and blood chemistry, including electrolytes, were performed before each cycle of chemotherapy. Chemotherapy was administered at full calculated dose unless ANC was less than 1500/uL or platelet count was less than 100,000/uL. For patients with Cr Cl between 40 to 60mL/min, carboplatin targeting an area under the curve (AUC) of 2mg/mL min (Calvert formula) was to be substituted for cisplatin. If Cr Cl dropped to less than 40mL/min or the patient developed otologic grade 3 or worse toxicity, cisplatin was stopped totally. Also, carboplatin was to be substituted for cisplatin in case of grade 2 neurological toxicity.

For radiotherapy, the patients were treated in the supine position. The neck was extended to move the oral cavity superiorly and to reduce dose to the mandible and salivary glands. The shoulders were extended as low as possible. CT slices 3–5 mm thick were obtained from the base of skull to the carina to allow assessment of lymphadenopathy. Palpable disease was marked with lead wire and parallel opposed anterior–posterior fields defined to cover the tumour and adjacent lymph nodes if required. The GTV was defined as the primary or residual tumour and involved lymph nodes (>10 mm short axis diameter). The GTV was expanded by 10mm isotropically to form the CTV. This CTV was edited to reflect local patterns of tumour spread (e.g. including adjacent muscles if invaded but edited off bone and air). There may be significant shrinkage of tumour during a long course of radiotherapy so it may be necessary to redefine the CTV on a new planning CT scan during treatment. The CTV was expanded by 3–5 mm to form the PTV depending on local assessment of systematic and random errors and likely organ motion. The radiotherapy was delivered with a highvoltage technique (6 MV photons). If the tumour had infiltrated superficial tissues, a bolus was used.

Symptomatic treatment was started as soon as pharyngoesophagitis occurred (grade 1). It systematically combined a proton pump inhibitor, antiinfective therapy in case of clinical mucositis, and steroids and analgesics for grade 2 pharyngoesophagitis. Radiation therapy interruptions or delays were permitted only in case of severe (grade 3or 4) neutropenia, or pharyngoesophagitis.

Consolidative chemotherapy

Four weeks after completion of concurrent chemoradiation, the patients underwent a re-staging work up including, history, physical examination, CT neck, and CT chest and upper abdomen. Bone scan and contrasted CT or MRI brain were indicated if the patient had symptoms or signs suggestive of bone or brain metastasis. In the absence of clinical or radiological evidence of progressive disease, consolidation docetaxel/cisplatin started 4 to 6 weeks after chemoradiotherapy at 75mg/m2 intravenously over 1 hour every 21 days for four cycles. Chemotherapy was administered only if the ANC was ³1500/uL and platelet count was ³100,000/uL. Otherwise, treatment was delayed for one week to allow haematological recovery.

Evaluation criteria

Tumor assessments were performed at baseline after surgery and every 6 weeks according to RECIST. Response had to be reconfirmed at least 4 weeks after first being noted.

Morbidity of treatment

Chemotherapy-related toxicities were recorded according to the National Cancer Institute Common Toxicity Criteria version 3.0 (17). Acute (< 90 days) and chronic or late (>90 days) radiation related toxicities were graded according to the acute and chronic Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG) (18).

Study endpoints:

Major end points of the study were median survival, median progression free survival and toxicity. The 2-year survival and 2-year progression free survival (PFS) were estimated using the Kaplan-Meier method. Survival was estimated from the date of first treatment day to death or last follow-up visit. PFS was estimated from the date of first treatment day to first evidence of disease progression

Results

Patient Demographics

The present study included 13 patients with pathologically proven ATC. The demographic baseline patients and disease characteristics including age, sex, ECOG performance status, prior goitre or WDTC, extent of the disease are detailed in Table (1). The median age was 62 years (range, 48-73). There were 8 (61.5%) females and 5 (38.4%) males. Eighty patients had good performance status (ECOG 0 and 1). Three (23%) patients had a prior history of goiter for at least 5 years. Two (15.3%) patients had a prior well-differentiated thyroid carcinoma; both of them were treated in the past with thyroid lobectomy or subtotal thyroidectomy, and ATC had arisen in the residual thyroid gland. Nine patients received surgery for their neck tumors. Synchronous distant metastases were found in 5 (38.4%) patients.

Efficacy evaluation

All patients had bidimensionally measurable disease on computerized

tomography (CT) scan at study entry. Table (2) shows the details of response after concomitant chemoradiation and at the end of the treatment. After concomitant chemoradiation, 7 patients (53.8%) achieved objective response [CR 1 patient (7.6%) and PR 6 patients (46.1%)]. Four patients (30.7%) had stable disease and 2 patients (15.3%) had progressive disease. At the end of treatment, 9 patients (69.2%) achieved objective response, [CR 2 patients (15.3%) and PR 7 patients (53.8%)]. The local control was assessed. Of the assessable 13 patients, 7 patients remained radiologically stable and were qualified as controlled local disease.

The median follow-up duration was 15 months (range from 6 to 30 months). The actuarial 2 year survival was 38.4% (Fig.1). The actuarial 2 year PFS was 30.7% (Fig. 2). The median survival was 16.8 months and the median PFS was 13.4 months. A total of 7 patients (53.8%) had treatment failure, 3 patients (23%) had neck failure, 2 patients (15.3%) had exclusively neck failure, and 1 patient (7.6%) had neck and distant failure. Four patients (30.7%) developed distant metastasis.

Adverse events evaluation

Acute toxicity is shown in Table (3). All the patients experienced mild to moderate degree (grade 1/2) of dysphagia during concomitant chemoradiation. Three patients (23%) developed grade 3 or 4 toxicity during concomitant chemoradiation (Table 3-A). Grade 3 and 4 anemia, neutropenia, vomiting, and pharyngoesophagitis, the most severe toxicities during concomitant chemoradiotherapy, developed in 23%, 15.7%, 15.7% and 7.6% of patients, respectively. One patient (7.6%) developed febrile neutropenia. One patient died from severe chest infection (pneumonia). Two patients (15.7%) had grade 3 late radiation esophagitis. No spinal cord complications had been reported. During consolidation chemotherapy, 5 out of 13 patients (38.4%) developed grade 3 or 4 toxicity (Table 3-B). Myelosuppression especially neutropenia, was common. Four patients (30.7%) developed grade 3/4 neutropenia, 2 of them (15.3%) developed febrile neutropenia. Grade 3/4 anemia and thrombocytopenia were recorded in 23% and 7.6% of patients respectively. Two patients (15.3%) developed grade 3 fluid retention that necessitated diuretic therapy.

Discussion

Management of ATC is particularly difficult because patients usually present with both extensive local disease and distant metastases (7,19-21). In fact, the tumor often grows during treatment and the cause of death for most patients is local tumor invasion. ATC survival is not affected by either radiotherapy or chemotherapy alone. A combination of surgery, chemotherapy, and radiotherapy (23-25) has been effective in some patients, both for survival and local disease control, and has prevented suffocation due to tumor invasion of the trachea (23, 24).

Venkatesh et al. (6) reported that, 11% of patients receiving both radiotherapy and chemotherapy survived for an average of 13 months. Tallroth et al. (24) divided 47 patients into 4 treatment groups. The first group received methotrexate and radiotherapy (30-40 Gy) and had a median overall survival of 9 months. The second group received bleomycin, cyclophosphamide, and fluorouracil and radiotherapy and had a median survival of four months. The third group received the same therapy as the second group with the addition of surgical resection; the median survival was also four months. The fourth group received doxorubicin, radiotherapy, and surgical resection and also had a median survival of four months. Of the 34 patients treated with bleomycin, cyclophosphamide, and fluorouracil and radiotherapy, only 11 died of local growth. Werner et al. (26) had similar results with a combination of chemotherapy and external beam radiotherapy. Mancusi et al. (27) compared, without regard to the type of surgery, the effects of chemotherapy plus radiotherapy with those of chemotherapy or radiotherapy alone. Survival was significantly better with the combination treatment. Schlumberger et al. (28) used two different prospective protocols to treat 20 patients. Patients younger than 65 years received a combination of doxorubicin (60 mg/m2) and cisplatin (90 mg/m2), and those older received mitoxantrone (14 mg/m2). Radiotherapy (17.5 Gy in seven fractions to the neck and the superior mediastinum) was administered between days 10 and 20 of the first four cycles of chemotherapy. Three patients survived longer than twenty months, and five patients had a complete response. No response was seen in patients with distant metastases. The treatment was effective for survival and local control, preventing death from local invasion. After making the diagnosis of ATC with fine needle biopsy or open biopsy, Tezelman and Clark (29) administered bleomycin one to two hours before each dose of radiotherapy and fluorouracil before every second treatment. Three weeks after this combination therapy, thyroidectomy was performed to remove as much tumor as possible, and then two to three weeks later, radiotherapy and chemotherapy were again administered. This method of treatment prevented recurrence of tumor in the neck, and no patient died of strangulation. Patient care requires close attention to pain control, maintenance of the airway, and other quality-of-life issues.

Because anaplastic thyroid carcinoma grows rapidly, hyperfractionated accelerated radiation has been used, sometimes in combination with chemotherapy. A Swedish group has used multimodality therapy including combined preoperative hyperfractionated radiation and chemotherapy, followed by surgical resection, postoperative radiation, and chemotherapy. Although this aggressive approach resulted in a local recurrence-free rate of 60%, the median survival was only 3.5 months, and 2-year survival was only 9%.(7, 29-31). De Crevoisier et al. (10) from France reported improved local control with a combination of surgery, chemotherapy, and hyperfractionated accelerated radiotherapy. Of 24 patients treated, local control was obtained in 19 patients (79%), but the median survival was only 10 months. Toxicities were common in patients treated with this protocol. The Grades 3 and 4 toxicities of neutropenia, pharyngoesophagitis, anemia, and thrombocytopenia were 73%, 33%, 27%, and 13%, respectively. This protocol achieved good local control at the cost of high toxicity. Death was mainly caused by distant metastasis (10). Other investigators also reported the results of hyperfractionated radiotherapy with chemotherapy, with local control rates ranging from 22% to 76%, and median survivals varied from 2.5 to 12 months. (28, 26, 32, 33)

The results of the present study revealed that the concomitant docetaxel/cisplatin and limited volume irradiation without elective nodal irradiation followed by 4 cycles docetaxel/cisplatin can be safely administered with median survival and PFS of 16.8 months and 13.4 months, respectively. These figures were compared favorably with the results of other series of concomitant chemoradiation (22-25) and series of concomitant chemotherapy and standard field radiation followed by consolidation chemotherapy that reported median survival of 4-12 months (6, 16, 26- 28).

In comparison to prior reports, our results are superior due to three inventions. First, an ATC usually cannot be resected completely because it is very invasive. Thus, surgical treatment is indicated primarily for relief of airway obstruction. Total thyroidectomy and radical neck dissection may have no advantage over a less aggressive surgical approach (34, 35). Our patients were subjected to debulking of the tumor which is considered adequate treatment. It is also adequate for a histologic examination. Local control of disease is an important

component of clinical management (36). Second, IMRT is not available in our center, However, we did not use the standard irradiation of ATC with the field typically extends from mastoid tip to aortic arch. The volume in our patients includes primary tumor, central nodal compartment, and areas with involved nodes only. No elective nodal irradiation. Third, we used docetaxel/cisplatin not only as radiosensitizers but also as adjuvant chemotherapy cycles. It is impossible to filter out individual versus combined effects of the three. What seems clear, however, is that these inventions appear collectively to have produced superior results to those previously attained.

Conclusions

Our report of locally advanced and metastatic ATC patients treated with limited field irradiation and aggressive combination chemotherapy demonstrates encouraging long-term survival with acceptable, although significant, toxicity. We believe that these data provide a compelling rationale for further investigation of this approach to treating a disease that has historically been otherwise met with very discouraging outcomes.

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Tables

Table 1. Patients and disease characteristics.

Characteristics	No of patients (%)
Age (years)	
Median	62
Range	48-73
Gender	
Male	5 (38.4)
Female	8 (61.5)
ECOG	
0	1 (7.6)
1	11(84.6)
2	1 (7.6)
Prior Goiter	3 (23.0)
Prior WDTC	2 (15.3)
Synchronous distant metastases	5 (38.4)
Lung	3 (23.0)
Bone	1 (7.6)
liver	1 (7.6)

Table 2. Clinical response after concomitant chemotherapy and at the end of treatment.

	No of patients (%)	
Response	Concomitant chemoradiation	Consolidation chemotherapy
Complete response (CR)	1 (7.6)	2 (15.3)
Partial response (PR)	6 (46.1)	7 (53.8)
Stable disease (SD)	4 (30.7)	1 (7.6)
Progressive disease (PD)	2 (15.3)	3 (23.0)

Figures

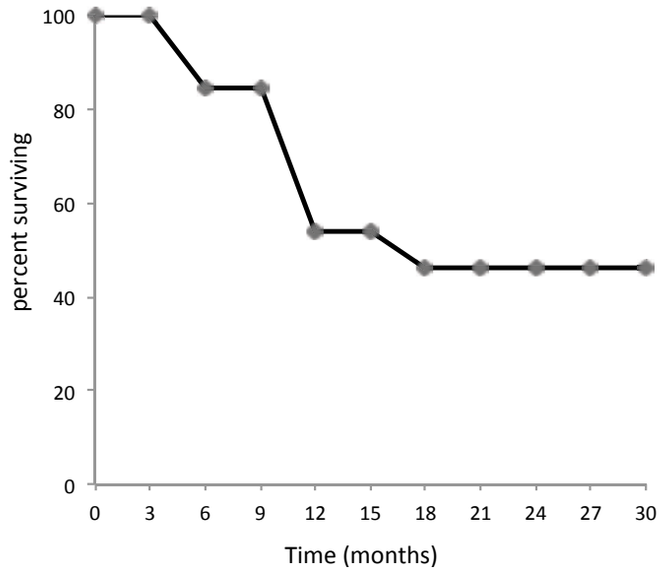

Fig 1: Actuarial survival.

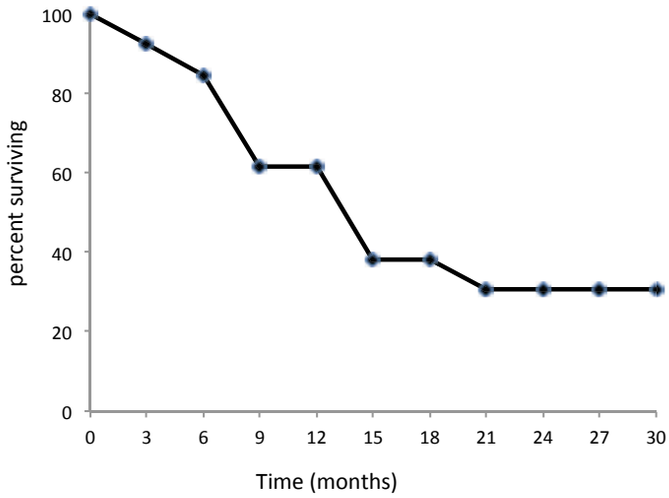

Fig 2: Actuarial progression free survival.