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Original Article

Metastatic and Adjuvant Colorectal Cancer Observational Study (MACRO Study)

Marwan Ghosn[1], Fadi El Karak[1], Joseph Kattan[1], Fadi Farhat[2], Joseph Makdessy[3], Georges Chahine[1], Ziad Salem[4], Abdalla Awidi[5], Hampig Kourie[6].

1. *Hotel Dieu de France Hospital*
2. *Hammoud Hospital University Medical Center*
3. *Saint George Hospital University Medical Center*
4. *American University of Beirut Medical Center*
5. *Jordan University Hospital*
6. *Saint Joseph Hospital*

Abstract

Background: Colorectal cancer (CRC) is a highly prevalent major health problem constituting 10% of all diagnosed cancers and 9% of all cancer deaths. Systemic chemotherapy for colorectal cancer is recommended as a post-operative adjuvant therapy for patients with early stages of the disease and as 1st line metastatic chemotherapy for those with advanced stage. The traditional regimen in the past decades included 5FU/ LV. However, addition of Oxaliplatin to the 5-FU/LV regimen improved the clinical outcome in early and advanced stages of colorectal cancer. This study was conducted to assess the therapeutic management of Oxaliplatin/ 5-FU based regimen in both adjuvant and first line metastatic therapy in non-selected patients from Jordan and Lebanon with early and advanced stages of colorectal cancers.

Methods: This was a multi-center, prospective, observational study that included patients with any stage of colorectal cancer whose physicians decided to treat with Oxaliplatin/ 5-FU based regimens as adjuvant or first line metastatic chemotherapy. All statistical tests were two-sided with a 5% significance level. Data was analyzed using SPSS (version 17). Adverse events were coded using MedDRA (version 18.0).

Results: 563 patients were included in the trial and 513 were eligible for analysis .The demographics of the patients and the characteristics of the tumors were comparable between the adjuvant and metastatic chemotherapy groups. The median age of the patients was 61.9 years, 57.3% were male and only 2.8% had an ECOG ≥2. 98.4% of the tumors were adenocarcinoma and around 70% were moderately differentiated. 55% of the patients were treated with Oxaliplatin/ oral 5-FU regimen and 45% with Oxaliplatin/ 5-FU; no significant difference was found between the adjuvant and metastatic chemotherapy groups regarding the used regimens. The median number of treatment cycles administered by patients in the adjuvant chemotherapy group (9 cycles) was significantly higher ($p=0.02$) than that of the metastatic chemotherapy group (8 cycles), without affecting the median treatment duration that was around 5 months in both groups. The median dose intensities of Oxaliplatin and 5-FU in the adjuvant chemotherapy group were significantly higher than those in the metastatic group ($p= 0.004$ and $p=0.001$ respectively).

77.9% and 13.4% of patients receiving adjuvant chemotherapy presented respectively an adverse event or a serious adverse event in the adjuvant setting, while 74.7% and 29.6% in the metastatic setting. The incidence rate of serious adverse events was significantly higher among the metastatic group compared to the adjuvant group (x% vs. y%, $p<0.001$). The most frequently reported non-serious events were peripheral sensory neuropathy (50.3%), nausea (23.1%), diarrhea (20.6%), anemia (17.1%), vomiting (15.8%), thrombocytopenia (13.3%) and neutropenia (9.6%). The most frequently reported serious events (other than disease relapse/ recurrence/ progression) were diarrhea (2.0%), vomiting (1.4%) abdominal pain (1.2%) and anemia (0.9%). Eight deaths were considered to be probably related to the chemotherapy treatment.

Conclusions

This trial revealed that oxaliplatin is administered at lower dose-intenstity and in fewer cycles in our studied population in Lebanon and Jordan. The incidence of peripheral neuropathy and other adverse events are lower in our population compared to those reported in the literature. Further prospective trials with long-term follow-up seem necessary to evaluate the impact of this clinical practice on the outcomes of the adjuvant and metastatic colorectal cancers.

Keywords

Colorectal Cancer
Oxaliplatin
5-Florouracil
Adjuvant therapy;
Metastatic chemotherapy
FOLFOX

Background

Colorectal cancer (CRC) is considered as a major health burden being the third most common cancer worldwide behind lung and breast cancers.(1,2) In 2012, 1.4 million cases were diagnosed with CRC all over the world (10% of all diagnosed cancers). In the same year, 694,000 people died from the disease. This accounts for 9% of all cancer deaths.(3) CRC cancer affects men and women of all racial and ethnic groups and more than 90% of cases occur in people aged 50 years or older.(4)

Based on the stage of the disease, the patient could undergo curative surgery. However, recurrence of CRC after 'curative' surgery is a major clinical problem. Systemic recurrence of the disease following surgery is more frequent than local recurrence and is very often the ultimate cause of death. This has justified the use of postoperative adjuvant chemotherapy.(5–7) Generally, adjuvant treatment is recommended for stage III and high-risk stage II CRC.

Post-operative adjuvant chemotherapy with 5-FU/ LV was used as the standard of care for patients with stage III colon cancer for a long period of time (8) . Actually, the standard of care following surgery is a doublet schedule with oxaliplatin and a fluoropyrimidine. The benefit of combination with oxaliplatin has been demonstrated in three landmark trials: MOSAIC study(9), NSABP C -07 (10) and XELOXA (11).

The same for patients with advanced colorectal CRC, the combination of 5-FU/LV was the standard of care, despite having no major impact on survival with an average median survival of 10 months. A new bench mark of survival for patients with metastatic colorectal cancer at around 20 months has been presented in many large prospective randomized phase III trials by adding oxaliplatin or irinotecan to the 5-FU/LV combination (12–15). ESMO Clinical Practice Guidelines for treatment of advanced colorectal cancer state that chemotherapy with FOLFOX regimen (5-FU/ LV/ Oxaliplatin) or FOLFIRI regimen (5-FU/ LV/ irinotecan) can improve the response rates, progression-free survival and overall survival compared to 5-FU/ LV regimen.(16)

The introduction of oxaliplatin, in the management of CRC in the adjuvant and metastatic setting, led to a change in the natural history of this disease. Years after the approval of this drug in daily practice, many trials, worldwide, aimed to evaluate and the therapeutic management of oxaliplatin-based regimens in real-life. No similar data was reported in the literature concerning the Middle East.

MACRO Study was carried out in several centers in Lebanon and Jordan in order to assess the therapeutic management of Oxaliplatin/ 5-FU based regimens in real-life as a post-operative adjuvant therapy in non-selected patients with early stages or as a first line metastatic therapy in non-selected patients with advanced stage of CRC. In addition, duration of treatment, dose intensity and patients' profile before treatment and at first relapse/ progression after initial chemotherapy and toxicity were assessed.

Methods

This was a prospective, multicenter, observational study that targeted patients with any stage of colorectal cancer for whom the investigator has decided to prescribe Oxaliplatin/ 5-FU based regimen as adjuvant or first line metastatic chemotherapy. This study was conducted from June 2008 (First patient in) to Oct 2015 (Last patient out).

Male and female patients, aged more than 18 years, suffering from colorectal cancer either early stage (after complete resection of primary tumor) or advanced stage (who have not received any previous chemotherapy for metastatic disease), for whom the treating physician decided to prescribe Oxaliplatin/ 5-FU based regimen upon his own discretion were considered for enrollment in the study after providing their written informed consent. While those with severely impaired renal function, myelosuppression and/ or hypersensitivity to Oxaliplatin, pregnant or lactating women and those who were participating in a clinical trial with any investigational drug used with a curative intent within 30 days prior to study entry were excluded.

The investigators who were invited to participate in the study were selected from all major centers at a country level among clinically experienced physicians who provide care to colorectal cancer patients in hospitals, academic and non-academic cancer centers, ambulatory care clinics/dispensaries and doctors' offices/ private practices.

Ethical considerations

This study was conducted in accordance with the principles of the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments. The ICH-E6 Good clinical practice guidance was followed.(17)

The study protocol, any amendments, accompanying material provided to the patient (informed consent) as well as any advertising or compensation given to the patient were submitted to independent ethics committees and/or institutional review boards for review and written approval.

Informed consent was obtained and documented prior to the conduct of any study-related procedures. The patient informed consent form was compliant to local regulations, ICH-E6 Good clinical practice requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information was given in a language and at a level of complexity understandable to the patient in both oral and written form by the investigator or designee. Each patient had the opportunity to discuss the study procedures and their alternatives with the investigator.

Prior to participation in the trial, the written Informed Consent Form was signed and personally dated by the patient or his legal representative and by the person who conducted the informed consent discussion (investigator or designee). The patient or his legal representative received a copy of the signed and dated Informed Consent Form. As part of the consent

process, each patient consented to direct access to his medical records for trial-related monitoring, auditing, EC review and regulatory inspection.

Data collection

Data was collected using paper case report forms (CRFs) in English. It was the investigator's responsibility to fill in the CRF and to record patient demographics, profile, relevant patient medical history, previous and current therapy, dose adaptation/ modification and follow-up.
Data was recorded at different time points; at the inclusion visit, before each treatment administration and during follow-up visits at 6 and 12 months after the last administration of chemotherapy.

All adverse events (AE) were managed and reported in compliance with all applicable regulations. All AEs regardless of seriousness or relationship to Oxaliplatin, spanning from the signature of the informed consent form until the end of the study for each patient were recorded on the corresponding page(s) included in the CRF. Specific pages were present in the CRF for the serious adverse events data collection. Reporting rules were planned to be done in an expedited manner. The computerized handling of data by DATACLIN CRO "Contract Research Organization" after receipt of the CRFs has generated additional queries to which the investigators responded by confirming or modifying the data questioned. These queries with their responses were appended to the paper CRFs.

Statistical Methods

Statistical analyses

All statistical tests were two-sided with a 5% significance level. Quantitative variables were summarized using: number of non-missing and missing data points for each parameter, mean, standard deviation, standard error, median, mode, minimum, maximum and 2-sided 95% CI of the primary and secondary variables.

Qualitative variables were summarized using number of non-missing and missing data points for each parameter and percentages with 2-sided 95% CIs for the primary and secondary variables. Missing data was not counted in the percentages.
Data was analyzed using SPSS (Statistical Package for the Social Sciences) software, version 17 (SPSS Inc., Chicago, USA, version 17).(18)

Adverse events were coded and presented according to MedDRA "Medical Dictionary for Regulatory Activities" version 18.0.(19)

Results

Patients' demographics and tumors characteristics:

The study was conducted in Lebanon and Jordan. 563 patients were first enrolled in this study; 513 (91.1%) were only eligible. 434 (84.6%) of the eligible patients were from Lebanon and 79 (15.4%) from Jordan. The different causes leading for the exclusion of 50 (8.9%) patients from the study are detailed in figure (1).

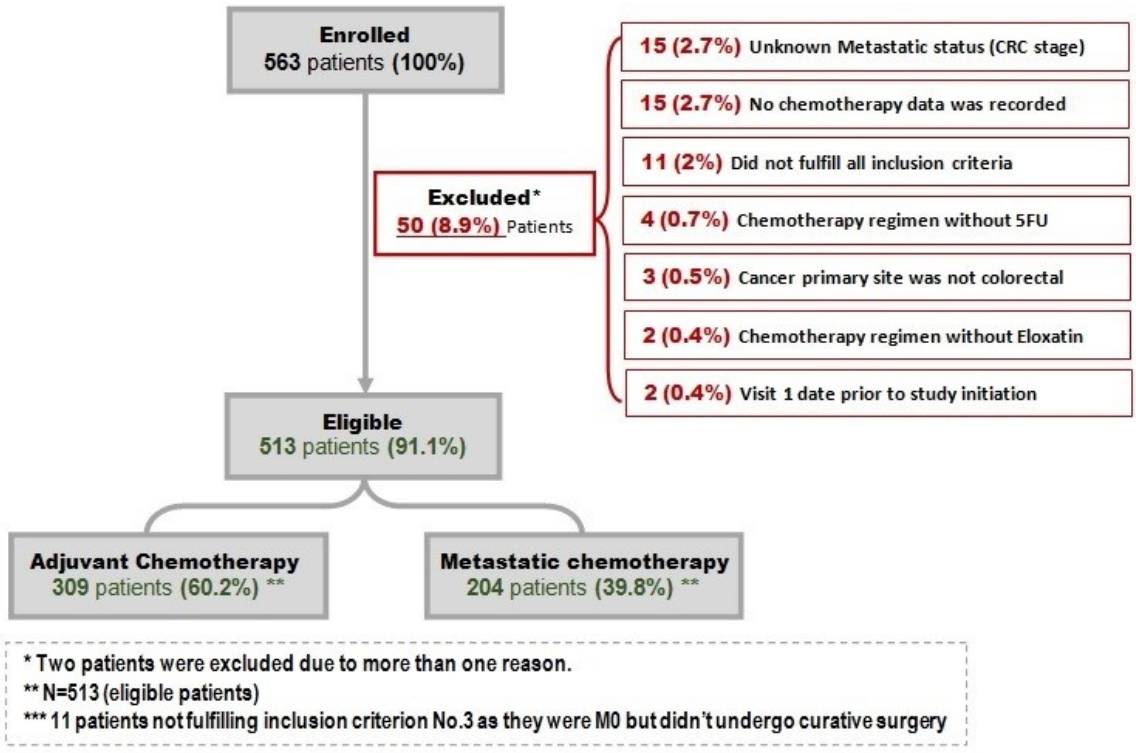

Figure 1. The different causes leading for the exclusion of 50 (8.9%) patients from the study

Out of 513 eligible patients, 309 (60.2%) received adjuvant chemotherapy for early CRC, while 204 (39.8%) received first line metastatic chemotherapy for advanced CRC.

The characteristics of the patients and tumors were comparable between the adjuvant and metastatic chemotherapy groups. The median age of the patients was 61.9 years, 57.3% were male and only 2.8% had an ECOG ≥2. 98.4% of the tumors were adenocarcinoma and around 70% were moderately differentiated.

Other than colorectal cancer, 184 patients (35.9%) have reported at least one past or current disorder/risk factor. Interestingly, 82 patients (16%) had a family history of malignant diseases and 20 (4%) had other malignant diseases.

Out of 513 patients, 452 (88.1%) were taking at least one concomitant medication during the study duration. Ranitidine was the most frequent medication used by 252 patients (49.12%).

Out of 513 eligible patients, 282 (55%) were on Oxaliplatin/ oral 5-FU regimen while 231 (45%) were on Oxaliplatin/ 5-FU based regimens. No significant difference was found between the adjuvant and metastatic chemotherapy groups regarding the used treatment regimens (p=0.876).

The median number of treatment cycles administered by patients in the adjuvant chemotherapy group (9 cycles) was significantly higher (p=0.02) than that of the metastatic chemotherapy group (8 cycles). However, no significant difference (p=0.382) was found between the median treatment duration in the adjuvant chemotherapy group (5.13 months) and that in the metastatic chemotherapy group (4.87 months).

The median dose intensity of Oxaliplatin, 5-FU and Leucovorin were 55.45, 836.99 and 156.63 mg/m²/2 weeks respectively. The median dose intensity of both Oxaliplatin and 5-FU were significantly higher in the adjuvant chemotherapy group compared to the metastatic group (p=0.004, p=0.001 respectively). No significant difference (p=0.889) was found between the median dose intensity of Leucovorin in the two settings.

Patients' profiles before treatment and at first relapse or progression:

Out of 309 receiving adjuvant chemotherapy, 59 (19.1%) have experienced disease relapse within 12 months of follow-up. The number of patients experiencing progression in the metastatic chemotherapy group was 119 (58.3%) out of 204 at 12 months of follow-up.

Regarding ECOG performance status score, results showed that the number of patients with ECOG 0 before treatment was significantly higher (p<0.001) than that at time of first relapse or progression while the number of those with ECOG 1, 2 or 3 was significantly higher (p<0.001) at time of first relapse or progression compared to that before treatment.

Safety Analysis:

77.9% and 13.4% of patients receiving adjuvant chemotherapy presented respectively an adverse event or a serious adverse event in the adjuvant setting, while 74.7% and 29.6% in the metastatic setting. In total, 430 patients experienced 1311 non-serious adverse events during the study duration. In addition, 113 patients experienced 168 serious adverse events.

The most frequently reported non-serious event was peripheral sensory neuropathy as reported in 283 patients (50.3%), followed by nausea in 130 patients (23.1%), diarrhea in 116 (20.6%), anemia in 96 (17.1%), vomiting in 89 (15.8%), thrombocytopenia in 75 (13.3%) and neutropenia as reported in 54 patients (9.6%). There was a difference of the non-serious adverse events in the adjuvant versus metastatic setting; for example, the incidence of peripheral sensory neuropathy in the adjuvant and metastatic setting is respectively 55.2% and 43.7%, nausea 25.1% versus 19.3%, diarrhea 21.2% and 18.8%, thrombocytopenia 15.8% versus 9.9%.

Regarding severity of the reported non-serious events; 930 (70.9%), 292 (22.3%), 61 (4.7%), 4 (0.3%) events were considered to be grade 1, 2, 3 and 4 respectively while the severity of 24 (1.8%) events was missing.

The majority of events, 1028 (76.8%), were considered to be likely related to chemotherapy; this finding was more pronounced in the adjuvant setting 646 (80.7%) than in the metastatic setting 348 (74.6%). Events with unknown relationship to chemotherapy (14 events, 8.3%) were counted as likely related to take the most cautious approach, as no data was available to support or deny the relationship to chemotherapy.

The treatment was more frequently permanently discontinued (5.3% versus 4.1%) or delayed (4.5% versus 3.1%) in the metastatic setting than in the adjuvant setting, while the doses were more frequently reduced in the adjuvant setting than in the metastatic setting (4.8% versus 2.3%).

The incidence rate of serious adverse events was significantly higher (p<0.001) among the metastatic group (29.6%) compared to the adjuvant group (13.4%). The most frequently reported serious event (other than disease relapse/ recurrence/ progression) was diarrhea as 11 events (2.0%) were reported. This was followed by 8 events (1.4%) of vomiting, 7 events (1.2%) of abdominal pain, and 5 events (0.9%) of anemia.

At the time of this report, most of the SAEs (60.7%) were recovered, 0.6% were recovered with sequelae, 3.6% were recovering, 25% were fatal (Out of them, 85% were not related to chemotherapy), 9.5% were not recovered while the outcome of 0.6% were unknown.

Out of 168 serious events, 98 (58.3%) were considered unlikely related to chemotherapy while 70 (41.7%), were considered to be likely related to chemotherapy. Events with unknown relationship to chemotherapy (14 events, 8.3%) were counted as likely related to take the most cautious approach, as no data was available to support or deny the relationship to chemotherapy.

A total of 55 cases of death (9.8%) were reported during the study. Of which, 41 deaths (7.3%) were reported in the metastatic group, 11 deaths (2.0%) were reported in the adjuvant chemotherapy group while the metastatic status of 3 patients (0.5%) was missing. Regarding causal relationship of death cas-

Table 1: Patient and tumor characteristics in the adjuvant and metastatic chemotherapy groups

	Overall	Adjuvant	Metastatic
Age (years)	61.9	61.4	62.1
Gender			
Male	(%57.3) 294	(%60.5) 187	(%52.5) 107
Female	(%42.7) 219	(%39.5) 122	(%47.5) 97
ECOG performance status			
0	(%75) 383	(%78.5) 241	(%69.6) 142
1	(%12.5) 64	(%10.1) 31	(%16.2) 33
2≤	(%2.8) 14	(%2.3) 7	(%3.5) 7
Undetermined	(%9.8) 50	(% 9.1) 28	(%10.8) 22
Histology			
Adenocarcinoma	(%98.4) 504	(%98.7) 305	(%98) 199
Mucinous colloid	(%0.8) 4	(%0.6) 2	(%1) 2
Other	(%0.8) 4	(%0.6) 2	(%1) 2
Differentiation			
Poorly differentiated	(%13.4) 68	(%12.3) 38	(%14.7) 30
Moderately differentiated	(%70) 355	(%71.1) 219	(%66.7) 136
Well differentiated	(%9.3) 47	(%10.1) 31	(%7.8) 16
Unknown	(%7.3) 37	(%6.5) 20	(%8.5) 17

Table 2: Therapeutic management of oxaliplatine/5-FU regimen, the duration of treatment and the dose-intensity

	Overall	Adjuvant	Metastatic
Treatment protocol			
Oxaliplatin/oral 5-FU regimen	(%55) 282	(%54.7) 169	(%55.4) 113
Oxaliplatin/5-FU based regimen	(%45) 231	(%45.3) 140	(%44.6) 91
Number of treatment cycles	8	9	8
Overall treatment duration (months)	5.1	5.13	4.87
Dose intensity mg/m2 per 2 weeks	55.4	58.1	52.8
Oxaliplatin	156.6	158.6	150.1
Leucovorin	837	883.8	779.4
5FU			

es, out of the 55 cases; 47 (8.3%) were considered as unlikely related to chemotherapy while 8 events (1.5%) were considered as likely related. Events with unknown causal relationship (5 events, 0.9%) were counted as likely related to take the most cautious approach, as no data was available to support or deny the relationship to chemotherapy.

It is also important to note that a significant difference (in all grades $p<0.005$, in grade 3 and 4 $p=0.013$) in neutropenia incidence (14.4% versus 7.05% in all grades, 3.29% versus 0.34% in grade 3 and4) was noted when comparing patients receiving FOLFOX to those receiving Eloxatine+5FU.

Discussion

The primary focus of MACRO trial was to record for the first time in the Middle East region (Lebanon and Jordan) how patients with adjuvant and metastatic colorectal cancer are treated with chemotherapy regimens including oxaliplatin in a real-life setting.

The evolution of adjuvant and metastatic systemic chemotherapy for colorectal cancer over the past decades led to the change of the natural history of this disease. This included the initial discovery of 5-FU, the enhancement of its cytotoxicity by Leucovorin, and subsequent addition of cytotoxic agents such as irinotecan, oxaliplatin and capecitabine. In addition to being the gold standard for care as adjuvant chemotherapy, the efficacy of FOLFOX regimen (5-FU, leucovorin and oxaliplatin) for the treatment of metastatic colorectal cancer has been proven. (20)

As choosing the best treatment regimen is a complex process that differs by institution, region, and country, this study was primarily conducted to asses in the current clinical practice the therapeutic management of Oxaliplatin/ 5-FU based regimen

and the duration of adjuvant and first line metastatic chemotherapy for early and advanced stages of colon cancer patients. Secondary objectives included the assessment of dose-intensity and comparing patients' profiles before treatment and at first relapse/ progression after initial chemotherapy. This was achieved through the primary and secondary analyses. This multicenter observational study was conducted in Jordan and Lebanon on adult patients with early stage colorectal cancer (receiving adjuvant chemotherapy) and those with advanced stage of the disease (receiving metastatic chemotherapy).

The tumors and patients demographic and clinical characteristics of our study were comparable to those reported in the literature. Concerning the therapeutic management of Oxaliplatin/5-FU based regimen, results showed that 55% of eligible patients were on Oxaliplatin/ oral 5-FU regimen while 45% were on Oxaliplatin/5-FU based regimen. The average duration of treatment was around 5 months. Moreover, the median number of cycles in our study was 9 cycles for the adjuvant treatment and 8 cycles for the metastatic setting. In comparison to our study, the number of cycles in the pivotal trial and in a similar trial in the literature was 6 to 8 cycles for oxaliplatin/ oral 5-FU and 12 cycles for oxaliplatin/5-FU for a total period of 6 months (9,21). In the metastatic setting, the number of cycles in the pivotal trial was also 12 cycles (13). This shorter treatment period and lower number of cycles in our study can be attributed to a tendency in Middle Eastern physicians to stop or delay the treatment to limit the side effects.

The median dose intensity of Oxaliplatin, 5-FU and Leucovorin were 55.45, 836.99 and 156.63 mg/m²/2 weeks respectively. The median dose intensity of both Oxaliplatin and 5-FU were significantly higher in the adjuvant chemotherapy group (p=0.004, p=0.001 respectively). Oxaliplatin administered dose intensity in our study is relatively low compared to doses reported in the literature (74 to 98 mg/m²/2 weeks).(22) This could be due to the long average duration of a treatment cycle in our study (2.5 weeks instead of 2 weeks) or because the physicians could have prescribed relatively low doses of chemotherapy in each treatment cycle. While for 5-FU, the observed median dose intensity is comparable to doses in the literature (bolus 297-338 mg/m2) followed by an infusion (467-510 mg/ m2/week).(23)

The safety of oxaliplatin/ 5-FU based regimens was assessed by tracking the occurrence of adverse events in enrolled patients throughout the study duration. The most frequent non-serious events included; peripheral sensory neuropathy, nausea, diarrhea, anemia, vomiting, thrombocytopenia and neutropenia. These side effects were similarly reported in the literature.

The incidence of peripheral neuropathy was around 55% in the adjuvant setting, which was less than the 90% reported in the MOSAIC trial (9). This is probably attributed to the lower dose intensity of oxaliplatin administered to our patients compared to the patients of MOSAIC trial. This is also confirmed by the fact that patients in the metastatic setting in our study had lower incidence of peripheral neuropathy compared to those in the adjuvant setting because of the lower dose-intensity of oxaliplatin. In fact, the incidence of peripheral neuropathy in metastatic setting was 68% in the pivotal trial and did not exceed the 42% of our trial (13). Concerning the other adverse events, the neutropenia was reported in less than 10% in the patients of our study compared to 70% in one of the pivotal trial (13). Lower incidence of diarrhea, thrombocytopenia, anemia and nausea was also noted in our study compared to the pivotal trial. The difference in the adverse event incidence in our study compared to the literature is most probably related to the lower dose intensity of oxaliplatin and fewer treatment cycles. Other hypotheses can also explain these discordant results with the literature going from the lack in reporting the adverse events or environmental or genetic predisposition to better tolerance of the treatment compared to other populations.

In consistence with the results of the current study, safety of FOLFOX4 regimen was assessed in a previous study and results showed that neurosensory adverse events, neutropenia, anemia, thrombocytopenia, nausea, vomiting and diarrhea were the most commonly reported adverse events with a difference in incidence of these side effects.(24)

Limitations

We acknowledge some limitations of the study. The long duration of recruitment and follow-up might have increased the heterogeneity of the studied population mainly in terms of disease management especially in the metastatic setting where several new molecules (targeted therapy) became a standard of care for the CRC management on top of chemotherapy.

Besides, the small sample size in Jordan makes it difficult to generalize the results to Jordanian population.

Conclusion

This trial revealed that oxaliplatin is administered at lower dose-intenstity and in fewer cycles in our studied population in Lebanon and Jordan. When comparing the administration of oxaliplatin in the adjuvant and metastatic setting, it was demonstrated that fewer cycles and lower dose-intensities of this drug were administered in the metastatic setting. The incidence of peripheral neuropathy and other adverse events are lower in our population compared to those reported in the literature. Further long-term prospective trials seem necessary to evaluate the impact of this specific practice on the outcomes of the adjuvant and metastatic colorectal cancers.

Disclosure

The authors do not have any conflict of interest regarding this work.

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