SAFETY AND EFFICACY OF OXALIPLATIN-BASED CHEMO-THERAPY IN THE FIRST LINE TREATMENT OF ELDERLY PATIENTS AFFECTED BY METASTATIC COLORECTAL CANCER

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies and the second cause of cancer death in the US and most European countries. Its incidence has been increasing in the last decades, primarily as a consequence of the aging of the population. In Europe more than 40% of new CRCs are diagnosed in patients older than 75 years.1,2 With an increasing number of elderly patients likely to be diagnosed with CRC in the upcoming decades, it is of interest how this population tolerates and responds to modern chemotherapy regimens.3

1Department of Medical Oncology, CRO Aviano National Cancer Institute, Aviano (PN), Italy
2Division of Medical Oncology B, National Cancer Institute, “Fondazione Pascale”, Napoli, Italy
3Department of Surgery, University of Catania, Policlinico Universitario “G. Rodolico”, Catania, Italy
4Division of Nuclear Medicine, CRO Aviano National Cancer Institute, Aviano (PN), Italy
5Division of Radiology, CRO Aviano National Cancer Institute, Aviano (PN), Italy

Corresponding Author: Massimiliano Berretta, MD; e-mail: mberretta@cro.it

ABSTRACT: Introduction: Elderly patients constitute a subpopulation with special clinical features that differ from those of the general population and are under-represented in clinical trials.

Materials and methods: We analyzed the toxicity and efficacy of an oxaliplatin-based chemotherapy (FOLFOX2, FOLFOX4 and XELOX) in the treatment of elderly patients affected by metastatic (m) colorectal cancer (CRC). One hundred and sixty-seven consecutive patients (FOLFOX2 20 patients; FOLFOX4 36 patients; XELOX 111 patients) aged 65 to 85 years (median age 75 years), 101 males and 66 females, with mCRC and measurable disease, were analyzed. The primary site of metastases was the liver (44% of patients). The majority of patients had a median performance status (PS) (ECOG) of 0 (range 0-2).

Results: The overall response rates according to the treatment schedules were: FOLFOX2 55%, FOLFOX4 44.4%, and XELOX 40.4%. The median progression-free survival (PFS) was about 7.3 months in all treatments and the median overall survival (OS) rates were: FOLFOX 2 21.8 months, FOLFOX4 16 months and XELOX 16 months. The main hematological and extra-hematological toxicities (grade 3 or 4) were neutropenia (14.4%), and neurological toxicity or diarrhea (15%). No toxic death occurred.

Conclusions: Oxaliplatin-based chemotherapy maintain its efficacy, and safety in elderly patients with mCRC and good PS. The different results in terms of PFS and OS, according to the treatment performed, could be dependent on the different number of patients enrolled in each study. This regimen should be considered in the treatment of this particular setting of patients.

KEY WORDS: Colorectal cancer, Elderly patients, Metastatic cancer, Oxaliplatin, Treatment.
In spite of these demographics, little is known about the impact of age on the morbidity of cancer treatment in elderly patients. Standard treatments for mCRC include palliative chemotherapy, with an expanding range of available options, but the evidence supporting these treatments derives from clinical trials where elderly or frail patients are under-represented. Several pivotal trials were restricted to patients younger than 75 years. However, even when a formal upper age limit was not an inclusion criterion, the recruitment of elderly patients was difficult, and the few included were highly selected.

Noteworthy, elderly patients are characterized by frequent incidence of age-related co-morbidities such as impaired renal, cardiac, and liver function, general decline in health, loss of autonomy, and cognitive impairment that may impact on the therapeutic decision.

Nevertheless, the treatment of mCRC in elderly patients is still a challenge, the overall therapeutic strategy in this population should be individualized, and a general consensus on how to treat elderly patients with mCRC is still far from being achieved. Given the great importance of elderly population with CRC, it is central to systematically assess the management of elderly CRC patients with modern chemotherapeutic regimens. Fortunately, in the recent period more attention has been dedicated to this particular setting of patients and it is notable in the English literature.

In particular, oxaliplatin- or irinotecan-based combinations have increased the treatment options for patients with mCRC. Various phase III trials showed improved progression-free survival (PFS), RRs, and overall survival (OS) when infusional 5-FU/LV was combined with oxaliplatin or irinotecan compared with 5-FU/LV alone. More recently, oxaliplatin-based combinations were shown useful and safe in selected elderly patients with mCRC.

Oxaliplatin- or irinotecan-based combinations have increased the treatment options for patients with mCRC. Various phase III trials showed improved progression-free survival (PFS), RRs, and overall survival (OS) when infusional 5-FU/LV was combined with oxaliplatin or irinotecan compared with 5-FU/LV alone. More recently, oxaliplatin-based combinations were shown useful and safe in selected elderly patients with mCRC.

We report our experience on the use of chemotherapy in elderly patients with mCRC. In particular, in this study we explore feasibility and safety of oxaliplatin-based chemotherapy in our cohort of mCRC elderly patients reporting data on treatment response, toxicity and survival.

**PATIENTS AND METHODS**

**Patients selection**

From March 1993 to December 2010, 167 consecutive patients affected by mCRC (histologically confirmed), with adequate organ functions (defined as less than twice the upper normal values of internal ranges), absence of major chronic diseases, bi-dimensionally measurable metastases evaluated by Computed Tomography (CT) scans and ECOG PS ≤ 2, were considered eligible for this study.

**Treatment schedule**

These different kinds of treatment were: FOLFOX2, FOLFOX4 and XELOX.

The FOLFOX2 regimen comprised oxaliplatin 100 mg/m² as a 2-hour infusion on day 1, leucovorin 500 mg/m² as a 2-hour infusion on days 1 and 2, followed by 5-fluorouracil 1.5 g/m² as a 22-hour infusion for two consecutive days; every 2 weeks.

FOLFOX4 regimen comprised leucovorin 200 mg/m²/day in a 2-hour infusion, followed by bolus 5-fluorouracil 400 mg/m²/day and 5-fluorouracil (600 mg/m²/day in a 22-hour infusion) day 1 and 2 every 2 weeks, plus oxaliplatin 85 mg/m² as a 22-hour infusion for two consecutive days; every 2 weeks.

The XELOX regimen comprised oxaliplatin 130 mg/m²/day 1 then oral capecitabine 1,000 mg/m² twice a day, from the evening of day 1 to the morning of day 15, followed by a 7-day treatment-free interval, in a 3-week cycle.

Capecitabine starting dose was reduced to 75% in patients with moderate renal impairment (30 mL/min ≤ creatinine clearance < 50 mL/min), and adjusted for adverse events of grade (G) 2 or of higher intensity, according to the literature. Oxaliplatin dose was reduced for severe vomiting, G3 or 4 thrombocytopenia, for G4 neutropenia, or for significant neurological toxicity. In case paresthesiae with functional impairment persistent between cycles, oxaliplatin was discontinued. The planned number of treatment cycles was 6; patients maintaining response or stable disease after the planned cycles could further continue treatment with the same regimen or with capecitabine alone. Also in...
the XELOX regimen, the patients could continue capecitabine mono-therapy after discontinuation of oxaliplatin for neurotoxicity, regardless the number of received cycles.

Treatment was maintained until either disease progressed or unacceptable toxicity appeared. Patients received antiemetic prophylaxis as routine practice of each participating center. The prophylactic use of colony-stimulating factors was not allowed.

The treatment was reduced to 75% of the calculated dose when hematological toxicity greater than G3 occurred.

**Evaluation during the study**

At baseline, patients underwent a clinical history and physical examination, blood counts, liver and kidney function tests and evaluation of electrolyte concentrations, and prothrombine time. ECG, and CT-scan of the abdomen and thorax were performed before treatment start.

During the treatment, blood counts were performed on day 7 of the first two cycles, and then at the beginning of each following cycle, together with blood chemistry. Tumor response studies were performed every 6 cycles or earlier in case of clinical deterioration.

**Safety and toxicity**

Tumor response was evaluated by investigators according to the response evaluation criteria in solid tumors (RECIST) at 3-month intervals until the disease progression or patient death. Toxicity was evaluated at the beginning of each cycle using the National Cancer Institute Common Toxicity criteria scale, version 2.0.

**Statistical analysis**

The PFS and OS times were calculated from the start of treatment until evidence of disease progression or death, respectively.

Data on response rates are expressed as the proportion of responders (complete response and partial response) in relation to all the other categories (stable disease, progressive disease and not classified).

Survival analyses were calculated according to Kaplan-Meier method and differences between subgroups were assessed by means of the log-rank test. In all cases, statistical significance was claimed as $p < 0.05$ (two sided).

**RESULTS**

Between March 1993 and December 2010, 167 patients were retrospectively evaluated. All patients were assessable for toxicity and antitumoral activity. Baseline patient characteristics are listed in Table 1. The majority of patients were male (60.4%). Median patient age was 75 years (range 65-85). Most patients had a median ECOG PS before treatment of 0 (range 0-2) (72.4%), and more than half had only one metastatic location. Liver was interested by metastases in 42.5% of the patients, lung in 13.7% of the patients, liver and lung, together, in 18.5% of the patients. Twenty-one percent of the patients had received adjuvant chemotherapy with fluorouracil plus leucovorin or oral fluoropyrimidines.

**Treatment compliance**

A total of 1250 chemotherapy courses were administered (332 FOLFOX2, 334 FOLFOX4 and 584 XELOX). Seventy patients (22.7%) and 5 patients, received 75% and 50%, respectively (14 and 5 patients in the FOLFOX4 and XELOX treatment, respectively, received 75% of dose, while 1 and 5 patients in the FOLFOX2 and XELOX regimens, respectively, received the 50% dose schedule).

**TABLE 1. CLINICAL FEATURES OF THE 167 PATIENTS WITH METASTATIC COLORECTAL CANCER**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>101 (60.4)</td>
</tr>
<tr>
<td>Female</td>
<td>67 (39.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>75 (65-85)</td>
</tr>
<tr>
<td>Primary tumor</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>156 (93.7)</td>
</tr>
<tr>
<td>Rectum</td>
<td>11 (6.3)</td>
</tr>
<tr>
<td>PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>121 (72.4)</td>
</tr>
<tr>
<td>1</td>
<td>37 (22.2)</td>
</tr>
<tr>
<td>≥2</td>
<td>9 (5.4)</td>
</tr>
<tr>
<td>Reduction dose (%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>87 (52.2)</td>
</tr>
<tr>
<td>75%</td>
<td>70 (41.9)</td>
</tr>
<tr>
<td>50%</td>
<td>10 (5.9)</td>
</tr>
<tr>
<td>Sites of metastasis</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>71 (42.5)</td>
</tr>
<tr>
<td>Lung</td>
<td>23 (13.7)</td>
</tr>
<tr>
<td>Liver and lung</td>
<td>31 (18.6)</td>
</tr>
<tr>
<td>Others</td>
<td>42 (25.2)</td>
</tr>
</tbody>
</table>


low-up of 27 months (1-124 months) at the time of analysis, the median PFS was 7.3 months (range 1-30), and the median OS time was 22 months (range 1-124).

**Prognostic factors**

Analyses of prognostic factors were studied in XELOX regimen, initial ECOG PS (0+1 vs. >2), histological sub-type (mucinosus vs. non-mucinosus), number and site of metastases (1 metastasis vs. 2 or more metastases and lung+liver vs. other), CEA value (normal vs. 2/3-fold normal value), comorbidities (no comorbidities vs. comorbidities), dose chemotherapy reduction (reduction vs. non-reduction) and age (75 years or more vs. more than 75 years old). No predictive factors for response were found. The same variables were analyzed for OS (Figure 3) and PFS (Figure 4), also including the response to treatment (CR or PR vs. SD and PD). We have found that the patients with a worse prognosis were the ones with more than one metastasis, elevated CEA value and those who have received a reduced dose schedule, verso those with one metastasis, normal CEA value and full dose schedule treatment.

**DISCUSSION**

In the ageing countries, CRC predominantly affects older people and produces a soaring demand for care in those patients. Although the median age of those diagnosed with CRC exceed 70 years both in Europe and in the US, elderly patients are scantily represented into clinical trials, with less than 20% rate included in the key studies. Chronologic age has been a major barrier for clinicians to offer the best treatment modalities to elderly population. However, chronologic age does not always correspond to real physiologic age. Aging is characterized by presence of co-morbidities such as diabetes, cardiovascular disease and by the development of physiologic changes in all organs which will affect how a chemotherapeutic agent is absorbed, metabolized and eliminated. However, increasing chronologic age does not equate to a uniform decline in physiologic reserve of all systems in all individuals. Elderly population is not homogenous in health status: some are healthy, while others are extremely frail, affected by one or more co-morbid diseases that may influence treatment tolerance. It’s important to notice that elderly patients are under-represented in clinical trials, but also that the few included share a good performance status, are highly functional and

---

**Safety**

The hematological and non-hematological toxicities of the patients are listed in Table 2. The main hematological toxicity was grade 3-4 neutropenia in 14.4% of patients. Among non-hematological toxicities neurological toxicity and diarrhea were the more frequent with grade 3-4 occurring in 8.4% and 6.6% of patients, respectively. Dysphonia was reported in 29 patients (17.3%). No deaths due to toxicity occurred.

**Response to treatment**

The 167 patients included in the study were considered assessable for response. Complete response was achieved in 18 patients (10.7%), and partial response was achieved in 66 patients (39.5%) for a total overall response rate of 50.2%. Disease response was assessed by CT scan after six cycles. Forty-seven (28.1%) patients achieved disease stabilization. Consequently, 78.3% of all patients included in the study obtained disease control.

**Survival analysis**

Figures 1 and 2 show the overall survival for FOLFOX2, FOLFOX4 regimens. After a median fol-

---

**TABLE 2. HEMATOLOGICAL AND NON-HEMATOLOGICAL TOXICITY BASED ON WHO CRITERIA OF 167 PATIENTS WITH MCRC**

<table>
<thead>
<tr>
<th>WHO grade</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>G1-G2</td>
<td>39 (23.3)</td>
</tr>
<tr>
<td>G3-G4</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
</tr>
<tr>
<td>G1-G2</td>
<td>44 (26.3)</td>
</tr>
<tr>
<td>G3-G4</td>
<td>24 (14.4)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>G1-G2</td>
<td>55 (32.9)</td>
</tr>
<tr>
<td>G3-G4</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>G1-G2</td>
<td>57 (34.1)</td>
</tr>
<tr>
<td>G3-G4</td>
<td>11 (6.6)</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>G1-G2</td>
<td>69 (41.3)</td>
</tr>
<tr>
<td>G3-G4</td>
<td>14 (8.4)</td>
</tr>
<tr>
<td>Hand/foot syndrome</td>
<td></td>
</tr>
<tr>
<td>G1-G2</td>
<td>47 (28.1)</td>
</tr>
<tr>
<td>G3-G4</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Mucosites</td>
<td></td>
</tr>
<tr>
<td>G1-G2</td>
<td>24 (14.4)</td>
</tr>
<tr>
<td>G3-G4</td>
<td>2 (1.2)</td>
</tr>
</tbody>
</table>
Data obtained from this selected studies can’t be extended to general population, without rough approximations.

In spite of the magnitude of the problem, the treatment of CRC in elderly patients remains a challenge. Notably, elderly patients are less treated with chemotherapy, both in adjuvant and palliative setting, than general population. This trend may be attributed to 1) few data on safety and feasibility of chemotherapy in CRC elderly patients that are often excluded from studies; 2) concerns about toxic effects of drugs influencing quality of life; 3) presence of multiple co-morbidities that may influence the treatment tolerance.

Palliative chemotherapy remains the mainstay of treatment for patients with non-resectable or mCRC. Systemic chemotherapy may prolong survival, decreases tumor-related symptoms, improves general wellbeing or maintains it for a longer period of time when compared with the best supportive care.

Ho et al reported that the use of palliative chemotherapy for mCRC seems to decline with age; while over 70% of patients younger than 70 years receive some chemotherapy for mCRC, only 43% of patients older than 70 years receive palliative chemotherapy. This trend has been recently confirmed by the Australian Cancer Registry. To support the use of chemotherapy in elderly patients, Cascini et al have already demonstrated that fit elderly patients with advanced cancer are not harmed by full doses of chemotherapy.
Several studies have shown that elderly patients obtain a similar benefit than younger patients\textsuperscript{4,21,44,45}. Moreover, overall available data suggests that toxicity does not seem to show different patterns in patients over and under 70 years\textsuperscript{8,18,46,47}.

More recently, many authors have reported the safety and the efficacy of oxaliplatin-based chemotherapy in the treatment of CRC (both adjuvant and palliative setting) elderly patients (Table 3)\textsuperscript{12,13,18,21,28,48}.

Initial studies\textsuperscript{14} reported an increase of gastrointestinal toxicity in patients older than 65 years of age with FOLFOX regimen and a small but significant increase in G3-G4 neutropenia and thrombocytopenia; but this has not been confirmed by later trials\textsuperscript{19,20,28}.

In a recent SEER analysis focused on older mCRC patients exposed to oxaliplatin and not included in clinical trials, no survival differences were noted, compared to similarly aged patients exposed to FOLFOX, with fewer adverse events and overall safer toxicity profile\textsuperscript{49}.

Furthermore, a reduction in the rate of these toxicities have been achieved remaining similar efficacy\textsuperscript{27,50} through several modifications in the FOLFOX regimen (fractionated oxaliplatin or dose reduction) or the association with neuroprotective agents.

In this study, we investigated activity and safety of oxaliplatin-based chemotherapy in the treatment of mCRC elderly patients. Results can summarize as follows.

Figure 3. Overall survival.
First, we obtained a complete response in 18 patients (10.7%) and a partial response in 66 patients (39.5%) for a total overall response rate of 50.2%. This outcome translated in a median PFS of 7.5 months and a median overall survival time of 22 months. These results are similar to those reported in the literature (Table 3) and suggest that combination chemotherapy should not be denied to elderly patients who have been selected carefully on the basis of PS and comorbidities, and who are willing to receive curative treatment for their cancer.

Second, among analyzed prognostic factors (including sex, age, initial ECOG PS, location of metastases, number of metastases, CEA value, dose chemotherapy reduction) only the number of metastases (>1) and the CEA value significantly influenced survival ($\chi^2 = 33.82; p < 0.0001$), similarly to general population.

Third, the main G3-G4 hematological toxicity was neutropenia (24 patients, 14.4%), while G3-G4 neurological toxicity and diarrhea (non-hematological) occurred both in 25 patients only (15%). Moreover, no patient was admitted to the hospital because of toxicity and no toxic deaths occurred. Unfortunately, no data reporting cancer-related fatigue have been analyzed.

Fourth, it is to point out that the patients included into this study are a subpopulation of elderly patients characterized by their good PS and free from the typical geriatric syndromes. As a consequence, our data corroborating the safety and
feasibility of oxaliplatin based chemotherapy in mCRC elderly patients should be extended with caution to the entire elderly population. Moreover, we hardly encourage studies including less fit and frail patients that represent a large part of elderly population affected by cancer.

CONCLUSIONS

Chronologic age should not be a limiting factor for the decision making process for patients with mCRC who are considering treatment with oxaliplatin based chemotherapy. In fact, elderly cancer patients represent a new challenge in the third millennium. Moreover, with the aid of pharmacogenomic tests, we can better select elderly cancer patients and related treatments. However, elderly patients should be individually examined for PS, the presence or absence of comorbid medical conditions, independence in activities of daily living and carefully assessed as concerns relative risks and benefits for treatment. Our data add to those in the literature that support the use of adequate chemotherapy for elderly patients in good clinical conditions. Careful monitoring for toxicity and rapid intervention with supportive care measures when toxicity occurs is also mandatory, particularly in elderly patients.

Conflict of interest statement:
None.

Acknowledgements
The authors thank Mrs. Paola Favetta, for her expert assistance in the preparation and correction of the manuscript.

TABLE 3. PUBLISHED DATA ABOUT OXALIPLATIN-BASED CHEMOTHERAPY IN ELDERLY PATIENTS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Regimen</th>
<th>Median Age (yrs)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comella et al. (2005)</td>
<td>m</td>
<td>XELOX</td>
<td>75</td>
<td>41</td>
</tr>
<tr>
<td>Kim et al. (2005)</td>
<td>m</td>
<td>FOLFOX4</td>
<td>75</td>
<td>43.8</td>
</tr>
<tr>
<td>Goldberg et al. (2006)</td>
<td>Adj + m</td>
<td>FOLFOX4</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Figer et al. (2007)</td>
<td>m</td>
<td>FOLFOX</td>
<td>77</td>
<td>59.4</td>
</tr>
<tr>
<td>Berretta et al. (2008)</td>
<td>m</td>
<td>FOLFOX2</td>
<td>73</td>
<td>55</td>
</tr>
<tr>
<td>Rosati et al. (2009)</td>
<td>m</td>
<td>XELOX vs. XELIRI</td>
<td>75</td>
<td>38</td>
</tr>
<tr>
<td>Sastre et al. (2009)</td>
<td>m</td>
<td>FUOX vs. XELOX</td>
<td>73</td>
<td>34.9; 38</td>
</tr>
<tr>
<td>Berretta et al. (2011)</td>
<td>m</td>
<td>FOLFOX4</td>
<td>72</td>
<td>44.4</td>
</tr>
<tr>
<td>Berretta et al. (2013)</td>
<td>m</td>
<td>XELOX</td>
<td>75</td>
<td>40.4</td>
</tr>
</tbody>
</table>

Notes: ORR = overall response rate; Adj = adjuvant; m = metastatic

References

fiorica f, berretta m, ursino s, fisichella r, liessi a, fiorica g, comella p, natale d, farris a, gambardella a, maiorino l, berretta m, bears a, frustaci s, talamini r, lleshi a, timmiri s, tirelli u. colorectal cancer in elderly patients: from best supportive care to cure. anti-cancer agents med chem 2013; 13: 1438-1443.

2. fager m, seymour m, homerin m, hniass a, cassidy j, boni c, courtes-funes h, cervantes a, freyer g, papamichail d, le bail n, louvet c, hender d, de braud f, wilson c, morvan f, bonetti a. leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. j clin oncol 2000; 18: 2938-2947.

3. douillard jy, cunningham d, roth ad, navarro m, james rd, karasek p, jandik p, iveson t, carmichael j, alaki m, griya g, awad l, rougier p. irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. lancet 2000; 355: 1041-1057.


5. berretta m, cappellani a, fiorica f, nasti g, frustaci s, fisicella r, bearz a, talamini r, lleshi a, tambaro r, cocciolo a, ristagno m, bolognese a, basile f, meneguzzo n, berretta s, tirelli u. folfox4 in the treatment of metastatic colorectal cancer in elderly patients: a prospective study. arch gerontol geriatr 2011; 52: 89-93.

6. berretta m, di benedetto f, di francia r, lo menzo e, palmeri s, de paoli f, tirelli u. colorectal cancer in elderly patients: from best supportive care to cure. anti-cancer agents med chem 2013; 13: 1332-1343.

7. berretta m, bearz a, frustaci s, talamini r, lambardi d, fratino l, lleshi a, bonanno s, sarada j, alki g, biondi g, lippe p. high activity and reduced neurotoxicity of bi-fractionated oxaliplatin plus 5-fluorouracil/leucovorin for patients with previously untreated metastatic colorectal cancer. j clin oncol 2000; 18: 3560-3568.


9. kim hj, oh dy, kim yj, han sw, choi is, kim dw, im sa, kim ty, lee js, heo ds, bang yj, kim nk. reduced dose intensity of folfox-4 as first line palliative chemotherapy in elderly patients with metastatic colorectal cancer: final results of the South Korean industry cooperative oncology group trial 0108. cancer 2005; 104: 282-289.

10. kimm j, oh dy, kim yj, han sw, choi is, kim dw, im sa, kim ty, lee js, heo ds, bang yj, kim nk. reduced dose intensity of folfox-4 as first line palliative chemotherapy in elderly patients with metastatic colorectal cancer. j korean med sci 2005; 20: 806-810.

11. liessi m, liessi a, cacopardo b, michieli m, berretta m. hematopoietic growth factors support in the elderly. hematopoietic growth factors: a trial on the impact of three different implementation strategies on antibiotic prescriptions. support care cancer 2004; 12: 465-469.


13. rupevero m, liessi a, cacopardo b, michieli m, berretta m. hematopoietic growth factors support in the elderly cancer patients treated with antibiotic chemotherapy. anticaner agents med chem 2013; 13: 1438-1443.

14. tao y, boyle s, pruitt r, macleod r, scholander p, hickman e, d'angelis d, conlon m, seymour m, hesselink m. also known as: counseling oncology patients on the use of antibiotics. j clin oncol 2004; 22: 1237-1242.

15. tao y, boyle s, pruitt r, macleod r, scholander p, hickman e, d'angelis d, conlon m, seymour m, hesselink m. also known as: counseling oncology patients on the use of antibiotics. j clin oncol 2004; 22: 1237-1242.

16. tao y, boyle s, pruitt r, macleod r, scholander p, hickman e, d'angelis d, conlon m, seymour m, hesselink m. also known as: counseling oncology patients on the use of antibiotics. j clin oncol 2004; 22: 1237-1242.


