ORIGINAL ARTICLE

Therapeutic efficacy and toxicity of bolus application of chemotherapy protocol in the treatment of metastatic colorectal cancer

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ABSTRACT

Aim To compare efficacy and toxicity of bolus application of chemotherapy protocol, oxaliplatin, fluorouracil (bolus), leucovorin (folfox) between two groups of patients in the therapy of metastatic colorectal carcinoma (mCRC).

Methods A total of 63 patients were treated for mCRC in the period January 2009 – January 2010 at the Department of Oncology of the Cantonal Hospital Zenica, Bosnia and Herzegovina (first group, 30 patients) and at the Department of Oncology of the Clinical Hospital Centre Bežanijska kosa in Belgrade, Serbia, in the period January 2005 – January 2006 (second group, 33 patients). The patients were treated according the same protocol, i.v. bolus infusion, but in different day intervals (D), 1, 8, 15/28 days or D1-D5/28 days, respectively. In all patients the following factors were analyzed: tumor response, overall survival (OS), progression free survival, hematological and non-hematological toxicity .

Results Colon was the primary localization in almost two thirds of patients. There was no statistically significant difference between the groups according to the age, hematological and non-hematological toxicity, as well as in achieved OS. Progression free survival expressed in months was in average 5 months though with a large range between minimal and maximal survival time.

Conclusion Both groups have shown equivalent efficacy to applied chemotherapy protocols. Overall survival in the two groups matched data from the literature. Further research should confirm success of the combination of chemotherapy protocols and their combination with the biological therapy.

Key words: oxaliplatin, therapeutic response, overall survival, toxicity

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Original submission:
29 December 2014;
Revised submission:
10 February 2015;
Accepted:
16 March 2015.

Med Glas (Zenica) 2015; 13(2):

INTRODUCTION

It is estimated that every year colorectal cancer (CRC) affects about 1.2 million people and around 609,000 die as a consequence of CRC (1). The incidence increases with age (2,3). Elevated rates of incidence were estimated in European countries - Bosnia and Herzegovina (30 in men, 19 in women). Geographical patterns of mortality partially follow incidence. Estimated age-standardized rates (European standard) of cancer mortality by sex, cancer site and country 2012 in Bosnia and Herzegovina were 19.8 in men; 11.7 in women (4). Based on the data of the Cancer Register for Central Serbia it can be estimated that every year 4000 persons are affected by CRC in Serbia. Standardized incidence rate in Central Serbia is 33 per 100,000 in men and 19 per 100.000 in women (5). Approximately 60% of diagnosed CRC cases develop *metastatic* disease. In the disease etiology three groups of risk factors can be mentioned: family history, life style and colon diseases (6). Among others, it is particularly important to mention familial adenomatous polyposis (FAP) in high-risk patients (7,8). It is believed that most colon cancers occur in a process of several levels or malignant transformation of adenoma through the process of activation of oncogenes and inactivation of tumor-suppressor genes, adenoma-carcinoma sequence (9). There are some opinions which negate so called malignant transformation of benign *polyps*, and it is believed that in most cases those are cancers from the very beginning -"wolves in sheep's clothing" (10). In cancer prevention stool tests performed once a year allow for early detection of cancer in 18-33%, sigmoidoscopy every five years in 34-55%, colonoscopy every 10 years in 75% of persons (11,12).

Surgical treatment is a basis for the treatment of malignant diseases of the lower part of gastrointestinal system. A type of surgical treatment depends on tumor location (13,14). Possibilities of chemotherapy in patients with metastatic colorectal cancer (mCRC) are today promising thanks to oxaliplatin, irinotecan, capecitabine (5-fluorouracil+oxaliplatin, folfox, and 5-fluorouracil+irinotecan, folfiri) (15). Advantages of the selection of one of the these two protocols have been examined in a study by Tourgand (CERCOR study) according to which there is no significant difference in the overall survival regardless of selected therapy. However, there is a clear difference in the profile of toxicity, which means that the expected undesired differences are adjusted to age and potential comorbidities. Irinotecan proved to be safer in patients of older age (16,17). Based on results of OPTIMOX 1 study, suspension of the treatment is recommended in patients whose response to the treatment has been achieved or there is a stable disease, and after 6 or more cycles of the first-line treatment with FOLFOX protocol.

In such patients a maintenance approach with Capecitabine_or "stop and go" is advocated for, i.e. absence of therapy until metastases reach the previous size (OPTIMOX 2 study) (18).

Studies examining three medicaments were published: combination of 5 FU, irinotecan and oxaliplatin (folfoxiri), which had some promising results though in certain younger populations of patients (19). Oral fluoropyrimidine (capecitabine) proved to be efficient and similar to 5FU/LV (5 fluorouracil /leucovorin), which is administered in a long-lasting iv and contributes to better quality of life (20). In the last ten years significant achievement has been made in the treatment of mCRC applying biological medicines. Target therapy needs to ensure simultaneous increase in efficiency and reduced toxicity of chemotherapy (21-23). In addition to numerous therapeutic protocols it is obvious that there is still no standardized therapy (24). Therefore, when it comes to the treatment of different subpopulations of patients with chemotherapy, it is necessary to select them according to numerous factors in order to achieve the highest possible number of patients to undergo curative R0 (clear margins post metastasectomy) liver resections or whose life will be prolonged to the maximum with significantly improved quality of life (24,25). The aim of this paper was primarily to compare efficacy of chemotherapy protocol of oxaliplatin, 5-fluorouracil (bolus), leucovorin (folfox) as a "modified protocol" in a three-week regimen (days), 1, 8, 15/every 28 days at the Oncology Department of the Cantonal Hospital of Zenica, with data of "modified folfox protocol" applied in five-day regimen of administering every 4 weeks at the Clinical Hospital Centre *Bežanijska kosa* in Belgrade. The secondary aim was to compare toxicity (hematological and non-hematological) of these two modes of bolus application of chemotherapy protocol (folfox protocol) in the

treatment of metastatic colorectal cancer (mCRC). The parameters followed in both groups of patients were: overall therapeutic response, time to progression of the disease, overall survival (OS), and toxicity per number of chemotherapy cycles.

PATIENTS AND METHODS

This retrospective study included 63 patients: first (research) group (30), and second (control) group (33) in the period of one year. The study was conducted at the Cantonal Hospital Zenica in the period January 2009 – January 2010 (30 patients, research group), and at the Clinical Hospital Centre *Bežanijska kosa* in Belgrade in the period between January 2005 and January 2006 (33 patients, control group). The study included patients who had a verified diagnosis of metastatic colorectal cancer, histologically identified as invasive adenocarcinoma. The research group was treated at the Oncology Department of the Cantonal Hospital Zenica. The control group consisted of patients with same pathohistological diagnosis, e.g. metastatic colorectal carcinoma with good performance status, who were treated at the Oncology Department of the Clinical Hospital Centre *Bežanijska kosa* in Belgrade, with the same chemotherapy protocol (folfox protocol) as bolus infusion, but with different regimens, i.e. administration time intervals.

In all patients the survival was calculated from the date of the first chemotherapy cycle until the date of death as a result of any cause, and if this information was not available, until the date of the last control examination.

All collected data were analyzed applying methods of descriptive and analytical statistics: $\chi 2$ test, T-test, U test, normal distribution test, Wilcoxon Signed Ranks test, Mann-Whitney, Spearman rank correlation were used for statistical analysis. The T-test was used to access the average patients' age, $\chi 2$ test was used to analyze the distribution of patients to subsets according to therapeutic toxicity, Mann-Whitney to analyze the distribution of patients to subsets according to therapeutic response, time to progression, and overall survival.

RESULTS

The study included 63 patients of average age of 60 years. The youngest patient was 34 years old, while the oldest one was 74 years old. There is no statistically significant difference between the groups according to the age (p=0.269). Average difference between groups was 2.6 years (Table 1). Colon was the primary localization in almost two thirds of patients. Susceptibility to colon localization was noticed in 42 (67.7%), while 20 (32.3%) patients had rectal cancer. As far as gender is concerned, there was no significant difference in the distribution of primary localization of cancer (p=1.000)

Table 1. Average age, median and variability of years of age in research and control group of patients

Group	No (%) of patients	Arithmetic mean	SD	Median	Minimum	Maximum
Research	30 (48)	61.57	9.035	63.00	44	79
Control	33 (52)	58.97	9.392	62.00	34	73
Total	63 (100)	60.21	9.243	63.00	34	79

Analyzing distribution of patients per groups in relation to toxicity by dividing them to those who had or had no therapy-related toxicity, there was no statistically significant difference between the groups (p=0.424) (Table 2).

Table 2. Distribution of patients per groups in relation to toxicity of the chemotherapy

Group of patients	No (%) of patients		
	Toxicity of therapy		Total
	NO	YES	
Research	11 (36.7)	19 (63.3)	30 (100)
Control	9 (27.3)	24 (72.7)	33 (100)
Total	20 (31.7)	43 (68.3)	63 (100)

In terms of therapeutic response, out of the total of 63 patients for whom data is available, only nine (14.8%) patients had partial remission (PR), (five patients in the examined and four patients in the control group). One patient in the examined group had complete remission, while the highest number of patients, 40 (65.6%; 22 in the examined and 18 in the control group) had the progression of the disease (PD) mainly after the third cycle. There was no statistically significant difference between the groups according to therapeutic response (p=0.431) (Table 3).

Table 3. Distribution of patients per groups in relation to therapeutic response

Group of patients	No (%) of patients				
	Therapeutic response				Total
	PD	SD	PR	CR	
Research	22 (73.3)	2 (6.7)	5 (16.7)	1 (3.3)	30 (100)
Control	18 (58.1)	9 (29)	4 (12.9)	0 (0)	31 (100)
Total	40 (65.6)	11 (18.0)	9 (14.8)	1 (1.6)	61 (100)

PD, disease progression; SD, stable disease; PR, partial regression; CR, complete response

The applied therapy protocol assured stable disease, in terms of response, only to 11 (18%) patients (p=0.431).

Duration of the response was 5 months in average, with a large range between the minimum and maximum. There is no statistically significant difference between the groups according to time to progression (p=0.880) (Table 4).

Table 4. Arithmetic mean, SD, median and variability of time to disease progression

Group of patients	No (%) of patients	Arithmetic mean	SD	Median	Minimum	Maximum
Research	30 (52)	6.00	5.699	5.00	3	33
Control	28 (48)	5.21	2.455	5.50	2	9
Total	58 (100)	5.62	4.420	5.00	2	33

The overall survival of patients in this study was 23 months (in average with standard deviation of 14.5). Due to high standard deviation, the best indicator of overall survival is median survival and it was 20 months (Table 5). Three patients had overall survival more than five years. There was no statistically significant difference in achieved overall survival (OS) in the two groups (p=0.840). Time to progression (TTP) was 5 months in average, though with a large range between minimal and maximal survival time.

Table 5. Arithmetic mean, SD, median and variability of patients' overall survival

Group of patients	No (%) of patients	Arithmetic mean	SD	Median	Minimum	Maximum
Research	30 (49)	21.30	10.668	21.50	3	40
Control	31(51)	23.94	17.588	18.00	8	76
Total	61 (100)	22.64	14.541	20.00	3	76

DISCUSSION

Chemotherapy protocols in the treatment of CRC are selected according to the National Comprehensive Cancer Network (NCCN) guidelines (26,27). With introduction of biological therapy (bevacizumab, cetuximab and panitumumab) with the chemotherapy protocols median survival higher than two years was achieved. Without treatment patients with metastatic colorectal cancer (mCRC) live in average for five to six months (15).

Usual protocols for the treatment of mCRC are given in bolus. Current standard protocol includes administration of continuous infusion in the period of 48 hours. Such application achieves better therapeutic effect (22:14 %), longer median survival (12.1:11.3 months; p=0.04) and reduction of myelotoxicity (4:31%) (15).

The patients of the first group, in the Cantonal Hospital of Zenica, received folfox bolus protocol in the three-week regimen: day 1 (D1); day 8 (D8); day 15 (D15) / every 28 days, and the patients of the second group at the Clinical Hospital Centre *Bežanijska Kosa*, Belgrade, received folfox-bolus protocol in the five-day regimen, D1-D5 /every 28 days. Protocol modification, which means chemotherapy administration via bolus in different time frames (D1-D5 e.g., D1, 8, 15, every 28 days) in analyzed groups vs standardized continuous protocols over 48 hours administration time, was applied to enable the application administration in the conditions of daily hospital with patients going home every day after the therapy, ambulatory patients or daily clinic patients, and it is very comfortable for patients.

Analyzing groups examined with stage IV disease (metastatic disease) it is crucial to set the implementation of systemic measures of primary and secondary prevention as a basic task of our health care system (28,29).

The patients in the examined sample received 4 cycles of chemotherapy in average.

Like any other chemotherapy, folfox therapeutic protocol also causes various side-effects.

The study results indicate that the majority of patients had therapeutic response within 6 months, which is statistically significant. Comparing the data from the literature it could be concluded that they match the overall survival in this study. Multidisciplinary decision and individualized approach are the main principles when treating this heterogeneous group of patients.

The study supports administration of both protocols in clinical practice, but when taking into consideration lowing of the costs and less patients' visits, three-day administration regimen, can be considered preferred.

It is the major conclusion of the study that there is a crucial need for implementing prevention methods (primary and secondary) for early screening and detection of colorectal carcinoma, which would bring a long term therapeutic effect when treating colorectal carcinoma, but would also lower the costs.

Further research would need to be directed towards combining chemotherapy medications

and different protocols with biological medicines, which could result in even higher overall survival and decrease in undesired effects.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

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Terapijska efikasnost i toksičnost bolusnih primjena hemioterapijskog protokola u terapiji metastatskog kolorektalnog karcinoma

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SAŽETAK

Cilj Uporediti terapijsku efikasnost i toksičnost bolusnih primjena hemioterapijskog protokola, oxaliplatine, fluorouracil (bolus), leukovorin (folfox), između dvije grupe bolesnika u terapiji metastatskog kolorektalnog karcinoma.

Metode Ukupno 63 bolesnika liječena su od metastatskog kolorektalnog karcinoma, u periodu od januara 2009. do januara 2010. godine, na Onkološkom odjeljenju Kantonalne bolnice Zenica, Bosna i Hercegovina (prva grupa od 30 pacijenata) i na Onkološkom odjeljenju Kliničko-bolničkog centra Bežanijska kosa u Beogradu, Srbija, u periodu od januara 2005. do januara 2006. godine (druga grupa od 33 pacijenta). Pacijenti su bili tretirani istim hemioterapijskim protokolom, i.v. bolus infuzije, ali u različitim vremenskim intervalima, D1, 8, 15/28, odnosno D1-D5/28 dana. Kod svih pacijenata analizirani su terapijski odgovor, ukupno preživljavanje (OS), vrijeme do progresije bolesti, kao i toksičnost.

Rezultati Primarna lokalizacija u skoro dvije trećine pacijenata bio je kolon. Nisu ustanovljene statistički značajne razlike između skupina prema dobi, u hematološkoj i nehematološkoj toksičnosti, kao ni u ukupnom preživljavanju. Vrijeme do progresije bolesti u mjesecima bilo je u prosjeku pet mjeseci, ali s velikim rasponom između minimalnog i maksimalnog.

Zaključak Ustanovljena je podjednaka efikasnost hemioterapije u obje grupe bolesnika. Ukupno preživljavanje u dvije grupe bilo je podudarno s podacima iz literature. Dalja istraživanja trebala bi potvrditi uspješnost kombinacije hemioterapijskih protokola i njihove kombinacije s biološkom terapijom.

Ključne riječi: oxaliplatin, terapijski odgovor, ukupno preživljavanje, toksičnost