Biochemical liver function test parameter levels in relation to treatment response in liver metastatic colorectal patients treated with FOLFOX4 with or without bevacizumab

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SUMMARY

Introduction Combined use of bevacizumab and conventional anticancer drugs leads to a significant improvement of treatment response in patients with metastatic colorectal carcinoma (CRC). Conventional treatment protocols exert undesired effects on the liver tissue. Hepatotoxic effects are manifested as a disturbance of liver function test parameters. The relation between clinical outcome and disorder of biochemical parameters has not been completely evaluated.

Objective The objective of our study was to examine whether clinical outcome in patients with liver metastatic CRC correlates with the level of liver function test parameters.

Methods The study included 96 patients with untreated liver metastatic CRC who received FOLFOX4 protocol with or without bevacizumab. Biochemical liver parameters were performed before and after the treatment completion. Treatment response was evaluated as disease regression, stable disease, and disease progression. The patients were divided into three groups according to the accomplished treatment response.

Results In the group of patients with disease regression the post-treatment levels of aspartate aminotransferase, alanine aminotransferase, and bilirubin were statistically significantly increased. In contrast to this, gamma-glutamyltransferase and protein post-treatment values were significantly lower in relation to initial values. In patients with stable disease, difference was found only in the level of proteins being lower after the treatment. In patients with disease progression, values of aspartate aminotransferase and bilirubin were significantly increased after completed treatment.

Conclusion Treatment responses are not completely associated with the level of liver function test parameters. The only parameter which correlated with treatment response is gamma-glutamyltransferase. Its decrease is accompanied with disease regression.

Keywords: bevacizumab; colorectal liver metastases; hepatotoxicity; liver function test parameters; treatment response

INTRODUCTION

Colorectal carcinoma is the second leading cause of cancer death among all malignant diseases [1, 2, 3]. Irinotecan- or oxaliplatin-based regimens combined with fluorouracil and leucovorin (FOLFOX4) are established as first-line conventional chemotherapy protocols for metastatic colorectal carcinoma (mCRC) [4–7]. The development and addition of novel biological therapy to standard anticancer agents have significantly expanded treatment options in these patients. Results of the performed studies have shown that the addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), to first-line standard chemotherapy treatment protocols in patients with liver mCRC remarkably improved their therapeutic effect. This is reflected in clinically significant improvement of treatment response rate as well as in overall and progression-free survival [8, 9, 10].

Conventional chemotherapies exert direct hepatotoxic effect. The production of free oxygen radicals is considered to be the key event in chemotherapy-induced hepatic injury, which is manifested as a disturbance of liver biochemistry parameter values, or it can be histologically confirmed [11–18]. However, except for studies' data which emphasize the clinical benefit of combined use of bevacizumab and conventional anticancer drugs, knowledge about their influence on liver function status is limited. So far there are no data about the association between treatment response and biochemical liver function status in patients treated with conventional anticancer agents with or without bevacizumab.

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OBJECTIVE

The objective of this study was to answer whether treatment responses correlate with the level of tested biochemical liver function tests parameters and how the addition of bevacizumab influences it. It has been found that in spite of the favorable therapeutic effect of the treatment, except for gamma-glutamyltransferase (GGT) level decrease, the other six liver function test parameters were unchanged or even aggravated.

METHODS

The study group consisted of 96 patients with histologically confirmed liver mCRC, one or more unidimensionally measurable lesions (>1 cm according to the RECIST 1.1 criteria) [19], without the possibility for curative liver resection. The diagnosis of potentially resectable liver metastatic disease was based on computed tomography (CT) scan evaluation. The patients were treated with FOLFOX4/FOLFOX4 + bevacizumab as a first line chemotherapy protocol. The treatment was conducted at the Institute for Radiology and Oncology in Belgrade, Serbia. Demographic and clinical data were obtained by reviewing medical records for period from January 2009 to December 2014.

The study included only patients with previously untreated liver metastatic disease. Prior chemotherapy and radiotherapy for CRC treatment was allowed if they were completed at least one month before the patient inclusion in the study. Other inclusion criteria were as follows: the Eastern Cooperative Oncology Group (ECOG) (Eastern Cooperative Oncology Group)performance status score of 0–2, >18 years of age, normal hematologic, liver, and kidney function, and no contraindications for the drugs administration. Exclusion criteria were the following: previous other malignant disease except cervical carcinoma *in-situ* and basal cell skin cancer, known brain metastases, and clinically significant cardiovascular disease. The study was carried out in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines and institutional ethics committee requirements. All the patients gave their written informed consent before their participation in the study.

The patients were assigned to FOLFOX4 or FOLFOX4 + bevacizumab treatment protocol according to physician decision. FOLFOX4 chemotherapy protocol consisted of a two-hour infusion of leucovorin (20 mg/m^2) followed by a 5-FU iv bolus (400 mg/m^2) and a 22-hour infusion (600 mg/m^2) during the first two days, with oxaliplatin (135 mg/m^2) as a two-hour infusion on day 1 of a two-week cycle. Patients additionally treated with bevacizumab received it on the first day of therapy in a dose of 5 mg/kg.

The duration of bevacizumab administration was determined by a physician decision. In a case of grade 2/3 of nonhematologic toxicity (mucositis, diarrhea, and proteinuria), the chemotherapy was delayed for one week or until the patient's full recovery. In patients with grade 4 of mucositis, diarrhea, proteinuria (nephrotic syndrome), hypertension, thromboembolic events, and grade 3/4 of hemorrhagic events, as well as in those with gastrointestinal perforation, the treatment protocol was stopped and such patients were excluded from the study. In case of hematologic toxic events grade ¾, the hematology parameters were determined daily and the treatment was postponed until the patient's complete recovery. Assessment of adverse events during the treatment was performed using National Cancer Institute Common Toxicity Criteria (version 2.0) [20]. Each patient received at least four and at most twelve cycles of certain chemotherapy protocol. Patients were followed up until the end of the treatment or until the disease progression and switch to a second-line treatment protocol.

Before their enrolment into the study, assessments of vital signs, ECOG performance status, height, weight, endoscopic and radiologic examinations (abdominal ultrasound, chest X-ray, and multislice computerized tomography were performed for all the patients. Routine liver function test parameters [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, GGT, lactate dehydrogenase] relevant for monitoring chemotherapy hepatotoxic effects, were performed before and after the completion of the treatment. Their determination was performed using commercial biochemical tests on the Advia 1800 (Siemens Healthcare GmbH, Erlangen, Germany) biochemical analyzer.

Treatment response was evaluated after every fourth cycle until the completion of the study treatment. Response Evaluation Criteria in Solid Tumors guidelines version 1.1 were used to define all the responses. They were determined as disease regression (complete or partial regression), stabilization, and progression of the disease. Tumor responses were assessed by members (surgeon, medical oncologist, radiologist, and pathologist) of the joint interdisciplinary committee for gastro-intestinal tumors of the host institutions, who were not involved in the study.

Assuming that the addition of bevacizumab to standard FOLFOX4 protocol would lead to moderate difference of values of some biochemical liver parameters between the two groups of patients (effect size 0.30), a minimum of 82 evaluable patients was required. Statistical analyses were performed by using commercially available SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA) software package. The intent-to-treat patient population included all the patients who participated in the study. The usual descriptive statistic parameters were used in statistical analysis of the obtained results (median with interquartile range 25–75 percentiles). Depending on the normality of distribution of the observed parameters, Student's t-test for dependent or independent parametric characteristics and Wilcoxon signed-rank test and Mann–Whitney U-test for non-parametric characteristics were performed.

RESULTS

All the included patients were treated and followed up in the study. There were 41 female (42.7%) and 55 (57.3%) male patients with median age of 60 years (range: 35–79

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years). Out of 96 enrolled patients, 52 (54.2%) were treated with combined use of FOLFOX4 and bevacizumab, while 44 patients (45.8%) received the FOLFOX4 protocol.

According to treatment response, the patients were divided into three groups: (1) patients with disease regression, (2) patients with stable disease, and (3) patients with disease progression.

Results of the study are summarized in Table 1 and Graphs 1, 2, and 3. The obtained results are given before and after the treatment.

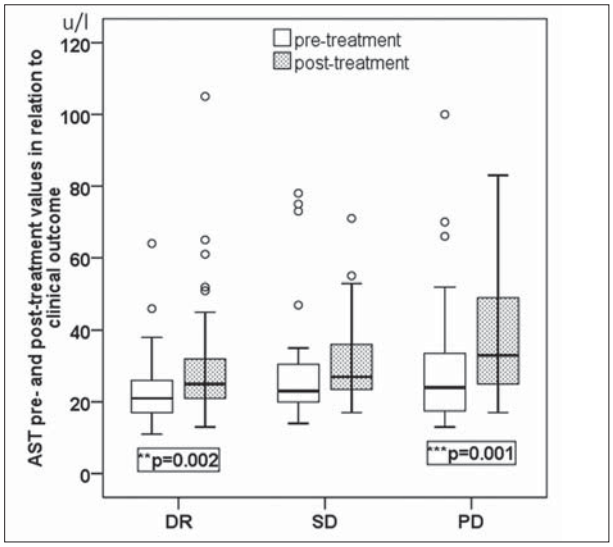
In the group of patients with disease regression as a post-treatment response, 7.3% achieved complete (CR) and 93.7% partial regression (PR) of the disease (not shown). Complete response was accomplished only in patients treated with combined use of FOLFOX4 and bevacizumab. At the same time partial regression was observed in patients on both treatment protocols, with the largest number of patients (68.2%) treated with FOLFOX4 + bevacizumab (not shown). Comparison of pre- and post-treatment values of tested biochemical parameters in these group of patients has shown that used anticancer agents led to the statistically significant increase in AST ($p = 0.002$), ALT ($p = 0.002$) and bilirubin ($p = 0.001$). In contrast to this, the level of GGT after the treatment was statistically significantly lower ($p = 0.035$) in relation to corresponding pre-treatment values (Table 1).

Table 1. Pre- and post-treatment values of biochemical liver test parameters in relation to clinical outcome in patients treated with conventional anticancer drugs (Group 1) and with bevacizumab added to conventional anticancer agents (Group 2)

Biochemical parameters	Value	Disease regression (n = 41)		Stable disease (n = 23)		Progressive disease (n = 32)	
		Pre	Post	Pre	Post	Pre	Post
AST (U/L)	Median	21	25**	23	27	24	33***
	IQR	17–26.5	21–33.5	20–32	23–36	17.2–33.7	25–50
ALT (U/L)	Median	21	26**	20	25	23	26.5
	IQR	14–30	18–38.5	17–31	19–29	18–34.7	20.2–40.2
ALP (U/L)	Median	86	95	122	105	134	142.5
	IQR	69–116	73.5–127.5	91–222	89–143	104–206	111–184.5
GGT (U/L)	Median	42	36*	77	61	87.5	77
	IQR	27–88.5	25–61.5	35–185	28–127	44.2–129.5	49–146.2
LDH (U/L)	Median	347	372	402	431	492	486
	IQR	288.5–387.5	325–419	347–926	345–624	320.2–944	432.5–732.7
Bilirubin (μmol/L)	Median	8.2	10.1**	8.6	10.1	8.4	11.8***
	IQR	6.9–11.1	7.2–13.7	6.9–14	7.5–13.3	6.3–11.2	8.9–15.6
Proteins (U/L)	Median	73	72*	74	71**	73	72
	IQR	71–76	69–73.5	71–78	70–74	70–76.7	68–75.5

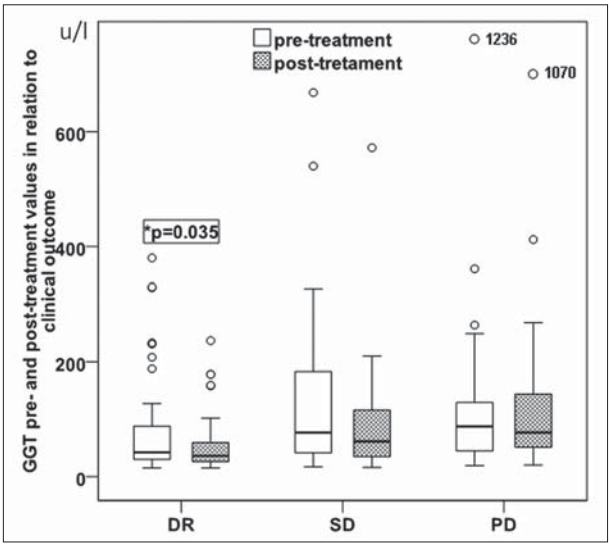
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$ intragroup pre- and post-treatment comparison

n – number of patients; AST – aspartate aminotransferase; U/L – units per liter; ALT – alanine aminotransferase; ALP – alkaline phosphatase; GGT – gamma-glutamyltransferase; LDH – lactate dehydrogenase; IQR – interquartile range



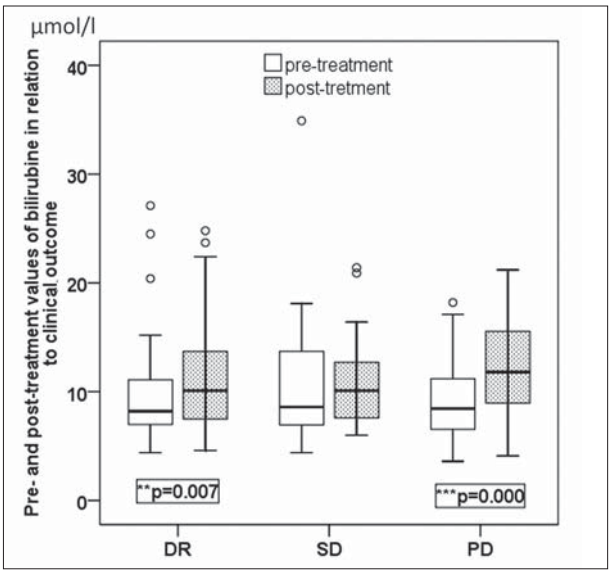
Graph 1. Pre- and post-treatment values of aspartate aminotransferase (AST) in relation to clinical outcome

** $p < 0.01$
*** $p < 0.001$ intragroup pre- and post-treatment comparison
DR – disease regression; SD – stable disease; PD – disease progression



Graph 2. Pre- and post-treatment values of gamma-glutamyltransferase (GGT) in relation to clinical outcome

* $p < 0.05$ intragroup pre- and post-treatment comparison;
** Extreme values of GGT in gruop of patients with PD are presented in the upper right corner
DR – disease regression; SD – stable disease; PD – disease progression



Graph 3. Pre- and post-treatment values of bilirubin in relation to clinical outcome

** p < 0.01
*** p < 0.001 intragroup pre- and post-treatment comparison
DR – disease regression; SD – stable disease; PD – disease progression

Of the 23 patients with stable disease, 56.5% (13 patients) received FOLFOX4 and the rest received FOLFOX4 + bevacizumab. The analysis of pre- and post-treatment results of tested liver function test parameters in these group of patients has shown that out of seven tested parameters, statistically significant difference was found only in the amount of protein. In this group of patients, as well as in those with disease regression, the level of protein after the treatment was statistically significantly decreased ($p = 0.012$ and $p = 0.010$, respectively).

Progression of the disease was much more pronounced in patients treated with FOLFOX4 chemotherapy protocol (71.9%). In patients with disease progression, an increase after the treatment was found in only two parameters – AST ($p = 0.001$) and bilirubin ($p = 0.000$) (Table 1).

Results of the intergroup analysis of difference of post and pre-treatment values have shown that statistically significant difference was found only in bilirubin values between groups with stable and progressive disease ($p = 0.017$) (not shown).

Pre- and post-treatment results of biochemical liver function test parameters were also compared between patients with the same treatment response, but on different treatment protocol. In this manner, groups comprising small number of patients were formed, which presents a limitation in presenting the obtained results. The results of the analysis have shown that there was no statistically significant difference between the tested parameters.

The absolute values of statistically significant results obtained after intragroup comparison of pre- and post-treatment values are graphically plotted (Graphs 1–3). Graph 1 shows that statistically significant difference between pre- and post-treatment results of ALT was found in groups of patients with disease regression and disease progression. Opposite to this, ALT pre- and post-treatment results in the group of patients with stable disease did not differ significantly. Graph 2 shows that statistically significant decrease of GGT post-treatment values was found only in the group of patients with disease regression. In two other groups of patients, no difference between GGT values before and after the treatment was found. Graph 3 shows that level of bilirubin after the treatment was significantly increased in patients with disease regression and in those with disease progression.

DISCUSSION

The results of the study have shown that combined use of bevacizumab and FOLFOX4 was oncologically more effective than FOLFOX4 alone, demonstrated by better treatment response. Namely, stabilization of the disease was prominent in FOLFOX4 chemotherapy protocol, while complete or partial regressions were inherent in FOLFOX4 + bevacizumab. These findings are consistent with the results of other studies which have examined the efficacy of bevacizumab added to conventional cytotoxic therapy.

Also, it was observed that both treatment protocols led to an increase of some of the tested liver function parameters (AST, ALT, and bilirubin). These findings might indicate that according to biochemical liver status there was no significant difference in chemotherapy-induced liver injury between these two treatment protocols.

On the other side, when levels of tested biochemical parameters were correlated with the treatment response, significant disparity was noted. Favorable clinical outcome did not always respond with the improvement of the tested liver function parameters. On the contrary, it was found that the most pronounced increase of liver biochemical parameters (AST, ALT, and bilirubin) was observed in patients with disease regression in comparison to those with stable or disease progression (AST and bilirubin). These findings demonstrate that both liver metastases as the basic disease and conventional anticancer agents used for their treatment have significantly impaired liver tissue as the result and lead to the disturbance of some of biochemical liver parameters.

Presented results of the study indicate that GGT is the only parameter which correlates with treatment response. Level of this enzyme is in relation with patients' clinical improvement being decreased after the treatment.

Several studies have shown a relation between FOLFOX4 chemotherapy protocol and severe hepatic injury manifested as hepatic sinusoidal obstruction syndrome or steatosis [21–28]. In these diseases it is not uncommon that biochemical parameters remain normal despite the underlying histopathological liver damage. Unique liver potential to regenerate and its capacity to compensate disruption of biochemical parameters could be a possible explanation for these findings [11–14]. In accordance with this are GGT results obtained in the study. Alongside clinical improvement, reduction of post-treatment GGT values may be a result of a liver compensatory mechanism. Nevertheless, several liver parameters were increased after the

treatment. The biggest concern that needs to be clarified is what causes such discrepancy between the levels of biochemical parameters. In other words, there is a dilemma as to why the value of one of the most specific liver parameter (GGT) is decreased in FOLFOX4 treated mCRC patients, while other parameters remain increased or unchanged.

CONCLUSION

To our knowledge, this is the first study to analyze the association between treatment response in patients with mCRC and biochemical liver function test parameters relevant for chemotherapy hepatotoxicity assessment. Recognizing GGT as a possible prognostic parameter for therapy effectiveness makes the study findings more important. However, it is necessary to conduct further investigations to confirm this claim.

NOTE

This paper is part of doctoral dissertation titled "Hepatotoxicity of combined conventiontional chemotherapy with or without biological therapy in patients with metastatic colorectal carcinoma" by M. Pharm. Kristina Denić.

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Ниво биохемијских параметара функционалног статуса јетре у односу на клинички одговор код болесника са метастатским колоректалним карциномом који су лечени *FOLFOX4* протоколом са бевацизумабом или без њега

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КРАТАК САДРЖАЈ

Увод Удружена примена бевацизумаба и конвенционалних антиканцерских лекова доводи до значајног побољшања клиничког одговора код пацијената са метастатским колоректалним карциномом (*CRC*). Конвенционални протоколи лечења испољавају нежељене ефекте на ткиво јетре. Хепатотоксични ефекти хемиотерапије се манифестују у виду поремећаја вредности биохемијских параметара функционалног статуса јетре. Корелација клиничког исхода и поремећаја вредности биохемијских параметара још увек није у потпуности позната.

Циљ рада Сходно наведеном, циљ нашег рада је да провери да ли клинички исход код *CRC* болесника са метастазама на јетри корелира са вредностима биохемијских параметара јетре или не.

Методе рада У студију је укључено 96 болесника оболелих од *CRC* са метастатским променама на јетри који су третирани *FOLFOX4* протоколом са бевацизумабом или без њега. Биохемијски параметри јетре су анализирани пре почетка и на крају спровођења терапијског протокола. Клинички одговор болесника је процењен као регресија, стабилизација или прогресија болести. Болесници су према постигнутом клиничком одговору подељени у три групе.

Резултати У групи болесника са регресијом болести ниво *AST*, *ALT* и билирубина на крају лечења је статистички значајно повишен. Супротно томе, вредности гама-глутамил трансферазе (ГГТ) и протеина након спроведеног лечења су статистички значајно ниже у односу на иницијалне вредности. Код болесника са стабилизацијом болести разликује се само ниво протеина, који је значајно нижи на крају лечења у односу на иницијалне вредности. Код болесника са прогресијом болести вредности *AST* и билирубина су биле значајно повишене након спроведеног лечења.

Закључак Клинички одговор код болесника са метастатским *CRC* није у потпуности у корелацији са вредностима биохемијских параметара јетре. Једини параметер који корелира са клиничким налазом је ГГТ. Смањење његове вредности праћено је регресијом болести.

Кључне речи: бевацизумаб; колоректалне метастазе на јетри; хепатотоксичност; параметри функционалног статуса јетре; клинички одговор

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