Splenomegaly During Oxaliplatin-based Chemotherapy for Colorectal Carcinoma

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Abstract. *Aim: The aim of this study was to evaluate changes in splenic size and platelet counts, in patients with colorectal cancer during oxaliplatin based chemotherapy, and to determine their clinical significance. Patients and Methods: The prospectively archived records of 50 patients with colorectal cancer that received oxaliplatin-based chemotherapy were reviewed. Results: Thirty-eight men and 12 women, of median age 58 (range 35-77) years, were enrolled. Median spleen volume ratios were 1.3-fold after 6 cycles and 1.9-fold after 12 cycles. The incidence of splenomegaly was 30% after 6 cycles and 67% after 12 cycles, and of thrombocytopenia was 70% after 6 cycles, 82% after 9 cycles, and 80% after 12 cycles. Thrombocytopenia was found to be related to splenomegaly, and this pattern was notable after 6 cycles of chemotherapy. Conclusion: Splenic enlargement and reduction in platelet counts were common during chemotherapy. Furthermore, these changes were found to occur rapidly after 6 cycles of chemotherapy.*

Oxaliplatin is a third-generation organoplatinum compound in which platinum is coordinated with diaminocyclohexane and oxalate, and which is active against colorectal carcinoma (1, 2). Since the US Food and Drug Administration first approved oxaliplatin for the treatment of metastatic colorectal cancer in 2002, oxaliplatin-based chemotherapy has been widely used to treat advanced colorectal cancer (3). However, decreases in platelet counts and increases in splenic size have commonly observed in patients with colorectal cancer on oxaliplatin-based chemotherapy. Although it is known that spleen size changes are due to oxaliplatin-induced sinusoidal injury (3), few reports have described the changing patterns of splenic size and platelet counts during chemotherapy, or their clinical significance. Thus, the aim of this study was to evaluate the changing patterns of splenic sizes and platelet counts and to determine their clinical significance during oxaliplatin-based chemotherapy for patients with colorectal cancer.

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Patients and Methods

Fifty patients with colorectal cancer, who received oxaliplatin-based chemotherapy (FOLFOX 4) in an adjuvant or palliative setting between November 2008 and June 2010, with data collated in a prospective database at the Colorectal Cancer Center, Konkuk University Medical Center, constituted the study cohort. Patients with a severe liver disease, such as active hepatitis, liver cirrhosis, or severe steatosis, as determined by laboratory or radiographic evaluations before chemotherapy were excluded. For patients administered palliative chemotherapy, those that had received another chemotherapy regimen within one year before study commencement were excluded. Radiological evaluations, which included abdominal and pelvic computed tomography (CT), and laboratory testing were performed after every three cycles of chemotherapy. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m), and these were used to divide the patients into three groups, namely the low BMI group (<20 kg/m^2), the normal BMI group (20 to <25 kg/m^2) and the high BMI group (≥25 kg/m^2).

FOLFOX 4 regimen. The oxaliplatin-based chemotherapy regimen (FOLFOX 4) was administered as a two-hour infusion of 85 mg of oxaliplatin per body surface area (BSA) on day 1 given at the same time as a 2-hour infusion of 200 mg of leucovorin per square meter of BSA using a Y infusion device. This was followed by a bolus of 400 mg of fluorouracil per square meter and a 22-hour infusion of 600 mg of fluorouracil per square meter on 4 consecutive days. These cycles were repeated fortnightly (4).

Measurement of splenic size. Computed tomographic (CT) data were transferred to a workstation equipped with software enabling automatic area measurements (Rapidia; INFINITT®, Seoul, Korea). Cross-sectional areas of spleen on each transverse CT scan (5 mm section thickness) were calculated by tracing the contour of the

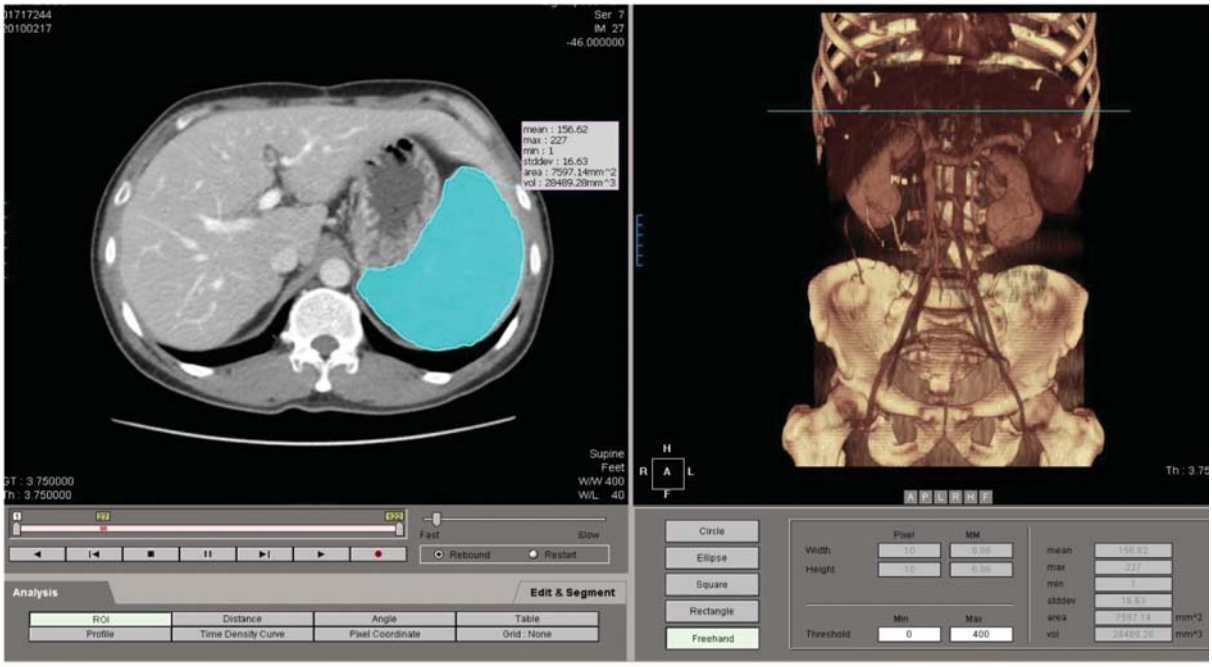

Figure 1. *Measurement of splenic size using Rapidia software (INFINITT, Seoul, Republic of Korea).*

spleen using an electronic free-curve provided by the software. Free-curves were drawn by a technologist experienced at computerized three-dimensional image processing, using an electronic pencil in the software package. Splenic volumes were calculated automatically by summing the area measurements of successive transverse CT scans (Figure 1). Splenomegaly was defined as a spleen volume of 50% greater than that of baseline.

Laboratory testing. Laboratory testing was performed at the same time as CT every three cycles. Thrombocytopenia was defined as a value below the normal reference range (140,000-400,000/μl).

Statistical analysis. Data analysis was performed using SPSS version 14.0 for Windows (SPSS Inc., Chicago, IL, USA). Summary statistics were compared using the two sample t- test with Welch's correction and Fisher's exact test. The relation between platelet count and splenic size changes was analyzed using Spearman's correlation. *P*-values of <0.05 were considered statistically significant.

Results

Fifty patients, 38 males and 12 females (median age=58.4, range=35-77 years) were enrolled. Thirty-one patients had colon cancer (62%) and 19 patients rectal cancer (38%). The majority of patients (94%) had stage III or stage IV disease. Adjuvant chemotherapy was performed for the majority of patients (72%). Patient characteristics are shown in Table I.

The median splenic size ratio increased with the number of chemotherapy cycles (Figure 2). The incidence of splenomegaly also increased with the number of chemotherapy cycles (Figure 3), reaching 67% after 12 cycles. Furthermore, the incidence of splenomegaly increased with chemotherapy cycle in each BMI subgroup, but no significant differences were found between BMI subgroups.

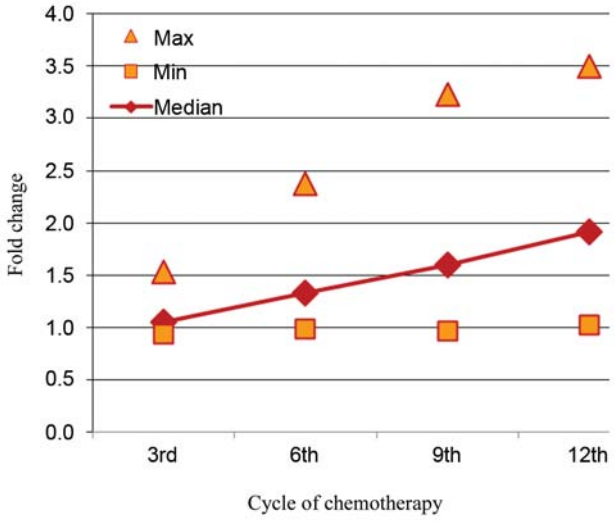

Figure 2. *Change in splenic size compared to pre-treatment baseline value by number of chemotherapy cycles.*

Changes in laboratory results, *i.e.*, in platelet count, aspartate transaminase (AST), and alanine transaminase (ALT), according to the number of chemotherapy cycles are shown in

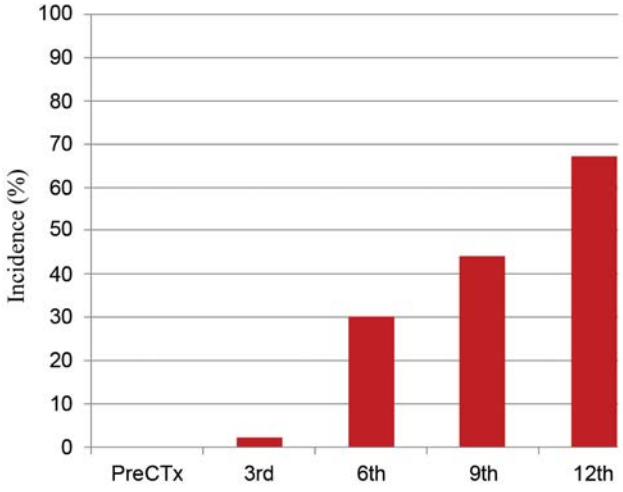

Figure 3. *Change in the incidence of splenomegaly by chemotherapy cycle number. PreCTx, Pre-chemotherapy.*

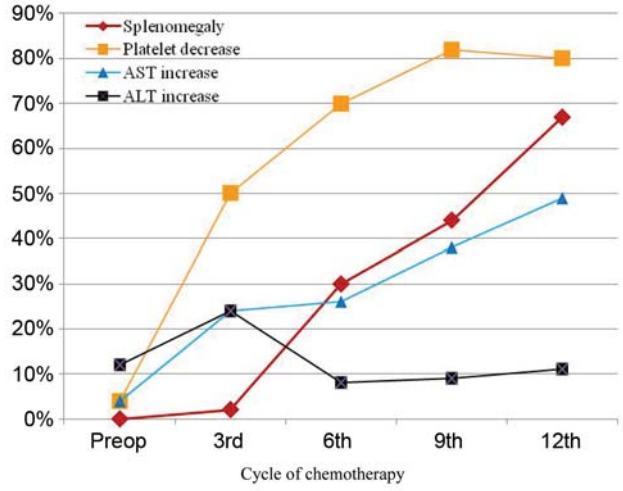

Figure 4. *Changes in laboratory findings by chemotherapy cycle number. Preop, preoperative status.*

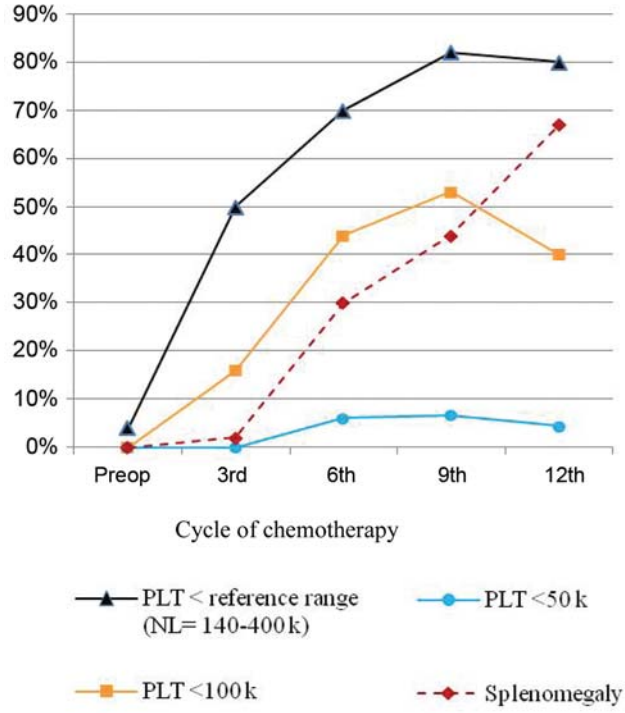

Figure 5. *Changes in the incidence of thrombocytopenia by chemotherapy cycle number. Preop, preoperative status; PLT, platelets.*

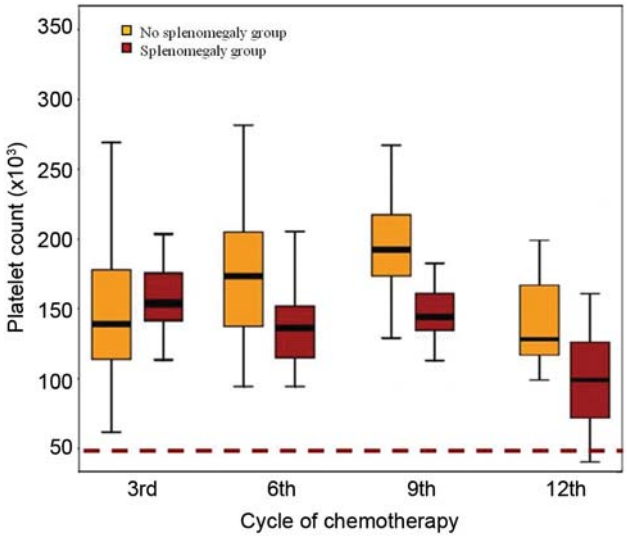

Figure 6. *Differences of median values of platelet count distributions between patients with and without splenomegaly.*

Figure 4. Notably, the incidence of thrombocytopenia increased with number of cycles, reaching 70% after 6 cycles, 82% after 9 cycles, and 80% after 12 cycles. Thrombocytopenia was found to be correlated with splenomegaly, and the correlation was very clear after 6 cycles (p=0.010). However, ALT and AST levels were not found to be significantly related to changes in splenic size (p=0.509 and 0.312), although AST level had a tendency to increase with increasing splenic size.

The patients were subdivided into three groups according to the degree of thrombocytopenia, namely <140,000/μl (140 k), <100 k and <50 k. The proportion of patients in each group by chemotherapy cycle number is shown in Figure 5. The incidences of a platelet count of <100 k reached 40% after 12 cycles, and the incidence of a platelet count of <50 k was 0% after 3 cycles, 6% after 6 cycles, 7% after 9 cycles and 4% after 12 cycles of chemotherapy.

When patients were divided into two groups according to the presence of splenomegaly, mean and median platelet

Table I. *Patient characteristics*.

Gender (M:F)	38:12	
Mean age (year) (range)	58.4±10.4	(35-77)
Colon:Rectum	31:19	62%:38%
TNM stage		
II	3	6%
III	33	66%
IV	14	28%
Aim of chemotherapy		
Adjuvant	36	72%
Salvage	14	28%
Mean height, cm (range)	163.6±8.8	(143-180)
Mean weight, kg (range)	66.0±11.4	(48-107)
Mean BSA, m^2 (range)	1.7±0.2	(1.4-2.2)

BSA: Body surface area.

counts in patients with splenomegaly were significantly lower than those in patients without splenomegaly (p=0.032). Furthermore, the range of platelet counts was lower in patients with splenomegaly, but platelet counts were greater than 30 k in all patients. These differences are shown in Figure 5.

Among the patients that underwent salvage oxaliplatin-based chemotherapy, five patients received 15 cycles, three patients 18 cycles, and one patient 21 cycles. All nine patients received more than 12 cycles of oxaliplatin-based chemotherapy, and median splenic size ratios were 2.6- fold after 15 cycles, 3.0- fold after 18 cycles, and 4.1- fold after 21 cycles. All nine of these patients had thrombocytopenia, but only one patient had a platelet count of <50 k (actually 38 k).

Discussion

Since Rubbia-Brandt *et al*. first reported a strong association between sinusoidal injury and oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer, an increase in splenic size has been accepted as a common finding of such therapy (5). However, few reports have addressed patterns of splenic size changes, the relation between these changes and platelet count changes, or the clinical significance of these changes.

To our knowledge, this is the first study to address splenic size changes measured by 3-D volumetry, platelet count change, and the clinical significance of spleen size changes during oxaliplatin-based chemotherapy for patients with colorectal cancer.

Our results show a 1.9-fold increase in splenic size and splenomegaly in 67% of patients after 12 cycles of oxaliplatin-based chemotherapy, which are high figures as compared with other reports. Overman *et al*. reported an increase in splenic size ratio of 22%, and an incidence of splenomegaly of 24% (3), and Angitapalli *et al*. reported an incidence of splenomegaly of 38% (3, 6). Two additional issues could be considered in this context, the method used to calculate splenic size and ethnic differences. In the past, splenic size was estimated using the splenic index (SI), *i.e*., splenic length (maximum longitudinal dimension) × splenic width (transversely across the hilum) × splenic height (cephalo-caudal dimension) (6, 7). However, the development of technologies like high resolution / thin slice computed tomography (CT) and associated software now allow accurate automatic measurements, which are more accurate than the above formula (8). Splenic size is related to height, weight, body surface area (BSA), and BMI (8), and in general, Caucasians are taller and heavier than Asians (13), and thus, given a lack of definite evidence, it might be presumed that spleens of Caucasian are larger than those of Asians (8). Furthermore, this difference in splenic sizes may have influenced observed splenic size changes.

According to the literature, histopathology associated with oxaliplatin-induced sinusoidal injury has many similarities to those seen in sinusoidal obstruction syndrome (3, 9). This syndrome, previously termed hepatic veno-occlusive disease, has features that include sinusoidal dilation, congestion, and subsequently, nodular regenerative hyperplasia, which are caused by disruption of the sinusoidal endothelium and subsequent collagen deposition, metalloproteinase-2 or 6 expression in the peri-sinusoidal space and the differentiation of endothelial cells into the sinusoid lineage (3, 9-11). Furthermore, the development of diffuse sinusoidal injury leads to noncirrhotic portal hypertension and results in the clinical presentations of splenomegaly, ascites, esophageal or hemorrhoidal varix with bleeding, and hyperbilirubinemia (3, 10, 12). For this reason, it has been suggested that splenomegaly might be a marker of oxaliplatin-induced hepatic injury in patients with colorectal cancer who underwent oxaliplatin-based chemotherapy (6). Our patients that developed noncirrhotic portal hypertension attributed to oxaliplatin had splenomegaly without ascites, esophageal or hemorrhoidal varix with bleeding, or hyperbilirubinemia.

Two hypotheses have been offered to explain the cause of oxaliplatin-induced thrombocytopenia. The first concerns the immediate suppression of the bone marrow during chemotherapy, and the second sinusoidal injury and the induced splenic sequestration of platelets (3). Nonetheless, the two mechanisms could affect the development of thrombocytopenia, the second mechanism could explain the association between splenomegaly and a decline in platelet count (3, 6). In general, it is known that myelosuppression follows an acute course, with maximal toxicity within 7 to 10 days of drug administration and rapid recovery thereafter (13). Because laboratory testing was performed immediately before the start of the next cycle in our study, the immediate suppression of the bone marrow by chemotherapy had

disappeared to some degree. Moreover laboratory testing after 12 cycles of chemotherapy was performed on two or three weeks after chemotherapy. Counting the platelet number after the twelfth cycle of chemotherapy with slightly longer interval than the previous 10 to 14 day interval between the laboratory testing and chemotherapy, our data demonstrated the relationship of splenomegaly and thrombocytopenia rather clearly. Therefore, thrombocytopenia was more prevalent in patients with splenomegaly, which may be explained by the sequestration of platelets in the spleen.

Generally, thrombocytopenia is associated with an increased risk of bleeding (14). The clinical manifestation of thrombocytopenia is mainly easy bruising, and spontaneous bleeding does not usually occur until the platelet count is less than 20 k (15). In the present study, thrombocytopenia was observed in 80% of patients after 12 cycles of chemotherapy. However, the platelet count of most patients with thrombocytopenia was between 50 k and 140 k, and no patient had a platelet count of less than 30 k or a bleeding complication. These results show that thrombocytopenia is commonly experienced, but not a serious problem in the patients on oxaliplatin-based chemotherapy if the platelet count is maintained over 20 k.

In patients with stage IV colorectal cancer with initially unresectable liver metastasis, hepatic resection can be performed by tumor down-sizing after neoadjuvant oxaliplatin-based chemotherapy. In these cases, the development of hepatic sinusoidal injury might be related to an increase in morbidity due to a greater need for blood transfusions, higher biliary complication rates, and longer hospital stays (3). In a number of case reports, mortalities caused by fatal hepatic failure after neoadjuvant oxaliplatin-based chemotherapy and hepatic resection have been reported (9, 14). In the present study, we included nine patients that underwent more than 12 cycles of oxaliplatin-based chemotherapy with palliative intent. All nine patients had splenomegaly, with a splenic size 4 fold larger maximally than baseline. Thus, in terms of salvage chemotherapy, in patients with stage IV colorectal cancer that have undergone more than 12 cycles of oxaliplatin-based chemotherapy, splenomegaly and thrombocytopenia are of clinical significance with respect to noncirrhotic portal hypertension and the influence of additional hepatic resection.

However, in colorectal cancer patients that have undergone 12 cycles of adjuvant chemotherapy, the clinical significance of splenomegaly and decline in platelet count is questionable, because in the present study, no complication related to bleeding or a clinical problem was encountered, although splenomegaly and thrombocytopenia were observed in 67% and 80% of patients retrospectively after 12 cycles of chemotherapy. Furthermore, it has been suggested that sinusoidal injury is dose- dependent and reversible (3, 6, 9). In other words, splenic size and platelet count could normalize gradually after chemotherapy. However, this has not yet been demonstrated.

In conclusion, in patients with colorectal cancer, an enlargement of the spleen and a decline in platelet count were commonly observed after oxaliplatin-based chemotherapy, and a sudden increase in splenic size and decrease in platelet count were evident after six cycles of chemotherapy. However, although most patients had thrombocytopenia after 12 cycles of chemotherapy, no thrombocytopenia-related complication was encountered, presumably because the number of patients with a platelet counts of <50 k was minimal.

Conflict of Interest Statement

Authors indicated no potential conflicts of interest.

Acknowledgements

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