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Research Paper

Serum Lactate Dehydrogenase Levels as a Predictive Marker of Oxaliplatin-Induced Hypersensitivity Reactions in Japanese Patients with Advanced Colorectal Cancer

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Abstract

Objective: Clinical laboratory test data obtained prior to treatments were previously analyzed from the standpoint of susceptibility to hypersensitivity reactions in patients treated with the platimun anticancer agent, oxaliplatin (L-OHP). In the present study, the time course from the first to last cycle of the treatment was additionally analyzed to determine a better predictor of these reactions.

Methods: A total of 20 laboratory test data were obtained from 108 Japanese patients with advanced colorectal cancer who were treated with the L-OHP-containing regimens, FOLFOX4 and/or mFOLFOX6. The averages and variation coefficients (CV%) of the data until the last cycle of the treatment were compared between patients with hypersensitivity reactions and those without.

Results: The average serum lactate dehydrogenase (LDH) level was lower in patients with grade 1/2 reactions (P=0.016), whereas its CV% value was higher in patients with grade 3/4 reactions (P=0.005) than in those without reactions. An increase in serum LDH levels was observed in some patients with grade 3/4 reactions as the cycle number increased, and thereafter hypersensitivity reactions occurred. This phenomenon was not always observed, but was never detected in patients with grade 1/2 reactions.

Conclusions: Serum LDH levels may be a predictive marker of hypersensitivity reactions in patients treated with L-OHP. Further extensive examinations with a larger number of patients are needed to establish a patient management strategy.

Key words: colorectal cancer, FOLFOX, oxaliplatin, hypersensitivity reactions, serum lactate dehydrogenase level

Introduction

Oxaliplatin (L-OHP) is a third-generation platinum anticancer drug, and L-OHP-containing regimens, including FOLFOX4 and mFOLFOX6, are currently standard treatments for colorectal cancer [1-5]. The dose-limiting toxicities of L-OHP were shown to be cumulative sensory neurotoxicity and neutropenia [1-3,5], whereas hypersensitivity reactions have been recognized as problematic with the increasing use of L-OHP in clinical practice [6-13]. Hypersensitivity reactions are an important adverse effect that may determine whether the treatment can be continued. We previously demonstrated that L-OHP-related grade 3/4 hypersensitivity reactions occurred immediately after the initiation of infusion, whereas grade 1/2 reactions did not [14]. A total of 20 laboratory test data obtained prior to the treatments were analyzed [15]. A lower serum level of lactate dehydrogenase (LDH) was found to be a risk factor for grade 1/2 reactions, while a lower monocyte count was a risk factor for grade 3/4 reactions [15]. These pretreatment markers may contribute to the better management of L-OHP-induced hypersensitivity reactions; however, the treatment has to be repeated several times if it is to be tolerated by patients. The cycle number, i.e., number of repetitions, averaged 7.1±4.2 (±SD, range: 1-19) in these studies. Laboratory test data were continuously obtained to assess the condition of the patient before and after each cycle of the treatment. These values often fluctuate and are used for decision-making regarding the postponement of the next cycle of the treatment. A more detailed assessment of laboratory test data from the first to last cycle of the treatment may provide a better predictor of hypersensitivity reactions, and an additional analysis was performed herein.

Methods

Laboratory test data were obtained from 108 patients treated with the FOLFOX4 and/or mFOLFOX6 regimens at either of the Labor Health and Welfare Organization Kobe Rosai Hospital, National Hospital Organization Kobe Medical Center, Kobe University Hospital, Kobe Red Cross Hospital, or Shinko Hospital, Japan, between April 2005 and March 2009. All patients had histologically or cytologically confirmed advanced or metastatic colorectal adenocarcinoma. Patients had received no prior chemotherapy or only one regimen with a washout period of more than 4 weeks after the final day of the previous treatment. Adjuvant chemotherapy performed more than 6 months previously was not counted as previous treatment. Further eligibility criteria included: 1) age of 20-75 years; 2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 3) life expectancy of 3 months or more; 4) adequate hematological (leukocyte count: 4,000/mm^3-12,000/mm^3, neutrophil count: 2,000/mm^3 or more, platelets: 100,000/mm^3 or more), hepatic (transaminases: 2.5 times or less the upper limit of normal, total bilirubin: 2.0 mg/dL or less), and renal (serum creatinine: less than the upper limit of normal) function; and 5) the ability to take oral medication. Depending on the clinical situation, patients who did not meet the criteria could be treated with L-OHP under the careful supervision of medical doctors. Patients were excluded if they had either brain metastases, a history of other neoplasms (except for cured nonmelanoma skin carcinoma or cured carcinoma *in situ*), a history of severe drug allergies, interstitial pneumonitis or pulmonary fibrosis, severe pleural effusion or ascites, active infection, bowel obstruction, diarrhea, and serious uncontrolled comorbidity or medical conditions. Pregnant or lactating women or women not using effective contraception were also excluded.

Hypersensitivity reactions were assessed and classified according to the National Cancer Institute Common Criteria (NCI-CTCAE v3.0). A total of 20 laboratory test data were compared between patients who exhibited hypersensitivity reactions and those who did not, including hematological parameters (erythrocyte count, hemoglobin, hematocrit, leukocyte count, neutrophil count, lymphocyte count, eosinophil count, basophil count, monocyte count, and platelet count), hepatic parameters (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, and alkaline phosphatase), serum LDH, renal parameters (blood urea nitrogen and serum creatinine), carcinoembryonic antigen, and CA19-9 antigen. This retrospective study was approved by the Institutional Review Board of each of the 5 hospitals. It should be noted that laboratory test data obtained prior to the first cycle of the treatment were analyzed in terms of susceptibility to hypersensitivity reactions [15]. In this study, the time course from the first to last cycle of the treatment was additionally analyzed to identify a better predictor of hypersensitivity reactions. Laboratory test data at the n-th cycle represented those from initiation of the n-th cycle to just before the initiation of (n+1)-th cycle of the treatment, and worst ones were adopted when they were measured more than 2 times. The averages and variation coefficients (CV%) of the data until the last cycle of the treatment were used for comparisons. Fisher's exact test was used for analysis of the contingency table. The unpaired Student's *t*-test/Welch's test or Mann-Whitney's *U* test was used for group comparisons, and after a Bonfer-

roni correction, P values of less than 0.05 were considered significant.

Results

The cycle number in patients with no, grade 1/2, and 3/4 hypersensitivity reactions is summarized in Table 1. No significant differences was observed among 3 groups (p=0.149, Fisher's). The cycle number at which grade 1/2 reactions occurred was 7.5±4.6 (range: 2-17), whereas it was 9.3±3.9 (range: 5-16) for grade 3/4 reactions. An additional cycle of the treatment was not performed when grade 3/4 reactions occurred, whereas it was possible for grade 1/2 reactions. The average values of hematological parameters and serum LDH levels are summarized in Table 2. Serum LDH levels were lower in patients with grade 1/2 reactions than in those with no reactions (P=0.016, Mann-Whitney's); however, no significant differences were observed in hematological parameters between patients with no and grade 1/2 reactions, or between those with no and grade 3/4 reactions. No significant differences were noted in the other parameters examined in this study between patients (data not shown).

Laboratory test data fluctuated extensively from the first to last cycle of the treatment. CV% values are summarized in Table 3. Among the 20 laboratory test data analyzed herein, the CV% value was the highest for the basophil count, followed by the eosinophil count, and neutrophil count. The CV% value of serum LDH levels was relatively low, and a correlation was observed with hypersensitivity reactions; the CV% value was higher in patients with grade 3/4 reactions than in those with no reactions (P=0.005, Mann-Whitney's). The difference between the maximum and minimum values was also higher in patients with grade 3/4 reactions (P=0.017, Mann-Whitney's), while no such relationship was found for the maximum values (P=0.060, Mann-Whitney's). The time courses of serum LDH levels in patients with grade 3/4 are shown in Figure 1, and are from all 10 patients and expressed as a function of the cycle number. Serum LDH levels were increased in 4 of 10 patients as the cycle number increased until grade 3/4 reactions manifested, and these phenomena reflected the higher value of CV% in Table 3. An increase in serum LDH levels before the manifestation of hypersensitivity reactions was not observed for grade 1/2 reactions.

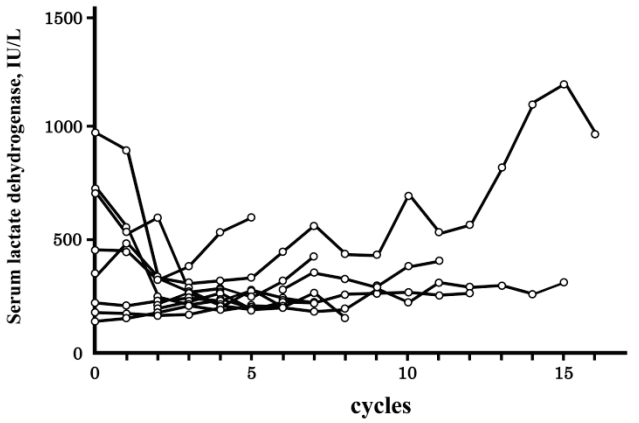

Figure 1. Time courses of serum lactate dehydrogenase levels in patients with grade 3/4 hypersensitivity reactions. Time courses are indicated as a function of the cycle number, i.e., the number of treatment repetitions. Grade 3/4 hypersensitivity reactions occurred in 10 of 108 patients treated with oxaliplatin, and the time courses of all 10 patients were indicated. The cycle number at which grade 3/4 hypersensitivity reactions occurred was 9.3±3.9 (±SD), and an additional cycle of the treatment was not performed.

Table 1. Cycle number of therapy in patients with no, grade 1/2, and grade 3/4 hypersensitivity reactions

	1-5	6-10	11-15	16-20
No hypersensitivity	38	31	13	2
Grade 1/2 hypersensitivity	4	6	3	1
Grade 3/4 hypersensitivity	1	5	3	1

No significant differences were observed among the 3 groups (p=0.149, Fisher's).

Table 2. Average values of hematological parameters and serum lactate dehydrogenase levels in patients with no, grade 1/2, and grade 3/4 hypersensitivity reactions

	No hypersensitivity N=84	Grade 1/2 N=14	Grade 3/4 N=10
Erythrocyte count, $\times 10^4$ /mm^3	372±52 [380, 37]	382±58 [392, 27]	398±45 [397, 17]
Hemoglobin, g/dL	11.3±1.8 [11.4, 1.3]	11.2±1.5 [11.1, 0.7]	11.7±1.8 [11.6, 1.3]
Hematocrit, %	34.3±5.1 [34.4, 3.5]	34.4±3.9 [34.6, 2.5]	35.9±4.2 [35.7, 2.4]
Leukocyte count, /mm^3	5039±3036 [4469, 834]	4457±1164 [4327, 775]	4877±1227 [4543, 324]
Neutrophil count, /mm^3	3082±3051 [2487, 672]	2325±1068 [2115, 869]	3056±1691 [2676, 357]
Lymphocyte count, /mm^3	1311±460 [1322, 336]	1450±390 [1424, 171]	1319±371 [1364, 187]
Eosinophil count , %	3.7±3.0 [3.0, 1.7]	6.0±5.5 [4.6, 1.7]	3.2±1.9 [2.6, 1.5]
Basophil count , %	0.7±0.5 [0.7, 0.3]	0.9±0.5 [0.8, 0.2]	0.8±0.5 [0.7, 0.2]
Monocyte count %	7.2±3.0 [7.2, 2.2]	6.8±2.7 [8.0, 1.6]	7.4±2.1 [7.7, 0.9]
Platelet count, $\times 10^4$ /mm^3	20.0±7.2 [19.3, 4.7]	17.4±6.0 [16.1, 2.7]	18.8±8.8 [15.3, 3.1]
Lactate dehydrogenase, IU/L	326±266 [240, 80]	241±172 [196, 22] *	336±132 [314, 79]

Values are the means ± standard deviations with the medians and quartile deviations in parentheses.
* significantly different from patients without hypersensitivity reactions

Table 3. CV% values of hematological parameters and serum lactate dehydrogenase levels in patients with no, grade 1/2, and grade 3/4 hypersensitivity reactions

	No hypersensitivity N=84	Grade 1/2 N=14	Grade 3/4 N=10
Erythrocyte count , %	7.8±5.9 [6.2, 2.3]	8.0±7.7 [6.2, 1.1]	7.6±6.1 [6.3, 1.0]
Hemoglobin, %	7.6±6.1 [6.0, 2.6]	8.1±8.1 [5.5, 1.4]	7.4±6.0 [6.1, 0.7]
Hematocrit, %	7.6±6.1 [6.5, 2.8]	7.8±7.7 [4.9, 1.6]	7.2±5.6 [6.0, 0.4]
Leukocyte count , %	31.6±18.5 [28.3, 10.2]	33.9±15.0 [31.1, 6.0]	32.9±9.0 [34.9, 6.6]
Neutrophil count , %	48.6±24.5 [45.8, 14.4]	52.9±25.6 [54.1, 13.0]	55.2±28.7 [54.3, 13.6]
Lymphocyte count , %	25.8±15.4 [24.3, 10.2]	21.4±7.3 [21.4, 4.9]	27.2±6.3 [27.4, 3.1]
Eosinophil count , %	52.0±23.8 [54.3, 17.3]	64.9±33.3 [67.3, 21.9]	47.2±21.4 [39.0, 17.9]
Basophil count , %	78.5±59.0 [68.9, 32.6]	74.0±52.9 [63.1, 18.9]	109.5±71.2 [87.9, 23.0]
Monocyte count , %	44.2±29.0 [41.0, 18.6]	51.2±32.0 [46.1, 13.1]	36.2±10.9 [35.7, 6.9]
Platelet count , %	31.1±15.9 [29.3, 10.6]	27.6±13.7 [26.5, 9.3]	31.4 ±8.7 [29.8, 5.1]
Lactate dehydrogenase , %	17.8±19.3 [16.4, 8.0]	14.8±12.6 [11.7, 3.6]	32.5±20.5 [22.4, 15.3] *

Values are the means ± standard deviations with the medians and quartile deviations in parentheses.
* significantly different from patients without hypersensitivity reactions

Discussion

Glycolysis, the transformation of glucose to pyruvate, is a key step for energy acquisition in all mammalian cells, including cancer cells. Pyruvate is further transformed to acetyl-CoA under normoxic conditions; however, suboptimal oxygen availability switches the metabolic pathway, resulting in the transformation to lactate via LDH-5, one of the 5 isoenzymes of LDH [16]. Immunochemical studies have shown that LDH-5 is overexpressed in non-small-cell lung cancer [17] and advanced metastatic colorectal cancer [18, 19]. Removal of the primary tumor was shown to result in a significant reduction in serum LDH levels in patients with non-small cell lung cancer [17]; however, serum LDH levels have not always reflected the presence of a tumor [20]. In spite of the lack of information on the relationships between serum LDH levels and presence of tumors, serum LDH levels have been investigated in terms of the response to treatment and prognosis of cancer patients [17, 21-25], and higher serum levels were concluded to be associated with a poorer prognosis. We previously demonstrated that a lower serum LDH level prior to the treatments was a risk factor for grade 1/2 reactions [15]. In this study, we analyzed laboratory test data from the first to last cycle of the treatment, and serum LDH levels were shown to be maintained at lower levels in patients with grade 1/2 reactions than those with no reactions (Tables 2 and 3). Our results suggest that patients without the exacerbation of tumors are susceptible to grade 1/2 reactions.

In our previous study, a lower monocyte count prior to the treatments was identified as a risk factor for grade 3/4 reactions [15]; however, no significant differences were observed in the average values between patients with no and grade 3/4 reactions (Table 2). In contrast, patients with grade 3/4 reactions could be characterized by larger variations in serum LDH levels (Table 3). As shown in Figure 1, serum LDH levels increased as the cycle number increased in some patients, and thereafter grade 3/4 reactions occurred (Figure 1). This phenomenon was not observed in patients with grade 1/2 reactions. If an increase in serum LDH levels suggests the exacerbation of a tumor, it is accompanied by grade 3/4 reactions.

Hypersensitivity reactions are a well-established complication of platinum agents; however, the mechanisms responsible remain unclear [26-29]. Reactions are thought to be mainly caused by the type I IgE-mediated system because they occur after multiple infusions; however, recent studies have suggested the contribution of the type IV T-cell-mediated system [26-29]. Regarding L-OHP, most reactions are thought to be of type I, while reports of hemolysis and thrombocytopenia suggest a type II reaction, and chronic urticaria, joint pain, and proteinuria can be attributed to a type III reaction [26-29]. In the present study, the CV% values of the eosinophil count were slightly higher in patients with grade 1/2 reactions ($p=0.082$), whereas those of the basophil count were higher for grade 3/4 reactions ($p=0.089$). Eosinophils and basophils are known to be involved in allergic reactions [30]. Eosinophils and basophils express many of the same receptors, whereas the cytokines produced differ [30]. The eosinophil and basophil counts may be predictive markers of L-OHP-induced hypersensitivity reactions.

In conclusion, a total of 20 laboratory test data were obtained from patients with advanced colorectal cancer who were treated with the L-OHP-containing regimens, FOLFOX4 and/or mFOLFOX6. The time course until the last cycle of the treatment was compared between patients with hypersensitivity reactions and those without. We demonstrated that the average value of serum LDH levels was lower in patients with grade 1/2 reactions, whereas its CV% value was higher in patients with grade 3/4 reactions

than in those without reactions. These results suggested that the serum LDH levels may be a predictive marker of L-OHP-induced hypersensitivity reactions.

Competing Interests

The authors have declared that no competing interest exists.

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