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Research Article

STAGE III COLORECTAL CANCER CASES SUCCESSFULLY COMPLETE 12 CYCLES mFOLFOX6 ADJUVANT THERAPY WITH THE REGULAR ADMINISTRATION OF GRANULOCYTE COLONY STIMULATING FACTOR SUPPORT

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ABSTRACT

It has been evaluated the impact of neutropenic events on the completion rate (Full administration of the planned dosage), and to review the use of G-CSF in standard adjuvant therapy for advanced colorectal cancer in this study. Data were collected retrospectively on four patients with colorectal cancer, who had been treated between April 1 2010 and June 30 2011 with mFOLFOX6 in our hospital. In each treatment, a blood examination was performed prior to treatment on the treatment day. Among the cases considered, there was no case in which administration of the drug was stopped due to adverse events other than hematotoxicity. Regarding hematotoxicity, G-CSF was administered in case of grade 1 adverse events, while it was withdrawn for a week in case of grade 2 or higher adverse events. In all cases, the treatment was completed in 12 cycles. There was no relapse during the therapy nor after the end of the therapy.We examined the adjuvant chemotherapy completion rates in a population of patients with stage III colon cancer to investigate the hypothesis that the same characteristics that predict differences in the initiation of adjuvant chemotherapy would predict the completion of a complete course of therapy. We identified the importance of the use of G-CSF in routine administration. Our routine G-CSF administration for mFOLFOX6 adjuvant therapy clearly contributed to the completion of the therapy.

Key words: G-CSF, mFOLFOX6, Filgrastim, Colon cancer

INTRODUCTION

The role of adjuvant chemotherapy in high-risk colorectal cancer has long been established, and its impact on survival is well recognized[1,2]. Equally important is the treatment of advanced or metastatic disease with chemotherapy for symptom control and survival benefit. mFOLFOX6 (a regimen infusion of l-leucovorin (LV) followed by a 5-FU bolus and infusion every 2 weeks, with oxaliplatin infusion) is the most common standard regimen for it[3].

The initiation of chemotherapy is, however, only the first step to improved survival. If groups that are less likely to initiate adjuvant chemotherapy also complete chemotherapy at lower rates, they will have an even greater survival disadvantage. There are few published studies on adjuvant chemotherapy completion rates for colon cancer. One randomized clinical trial showed a completion rate of 69%, but predictors of completion have not been studied intensively[4]. Neutropenia is one of the adverse events for dose reduction or treatment interruption.

Routine use of granulocyte colony stimulating factor (G-CSF) is not recommended, although many studies have confirmed the usefulness of primary growth factor support in maintaining dose intensity(DI)[5]. The American Society of Clinical Oncology (ASCO) guidelines in 2000 recommend the use of G-CSFs as a secondary prophylaxis to protect and prevent a new episode of febrile neutropenia or dose modifications where patients have experienced these complications with their first cycle of treatment.

The aim of the audit was to record the incidence of neutropenic events in patients undergoing chemotherapy, to evaluate the impact of neutropenic events on the completion rate, and to review the use of G-CSF in standard adjuvant therapy for advanced colorectal cancer.

MATERIALS AND METHODS

Study Design and Patient Selection

Data were collected retrospectively on four patients with colorectal cancer, who had been treated between April 1 2010 and June 30 2011 with mFOLFOX6 (regimen 2-hour infusion of l-LV 200 mg/m^2 or dl-LV 400 mg/m^2 followed by a FU bolus 400 mg/m^2 and 46-hour infusion 2,400 to 3,000 mg/m^2 every 46 hours every 2 weeks, with oxaliplatin 100 mg/m^2 as a 2-hour infusion on day 1)[3,6] in Ibaraki Prefectural Central Hospital. This site is instructed to obtain appropriate local institutional review board approval and is encouraged to use experienced oncology nurses, pharmacy personnel, or data management staff to collect the data. In case an adverse event of grade 3 or 4 occurred during the treatment, G-CSF was given on the scheduled administration date and the administration was postponed for one week. For these cases, G-CSF was given one week before the scheduled administration date, and in the cases in which administration was thus possible, this manner of administration was continued, but if administration was hindered by adverse events, G-CSF was given, in principle, one week or six days before the scheduled date. Administration was continued in principle until disease progression developed or until the onset of a serious adverse event. The result was serious thrombocytopenia in two cases during the second and fifth courses of the treatment, respectively, so administration was suspended and the regimen was changed. In the other cases, administration was continued as shown in the table. We defined the completion chemotherapy as Full administration of the planned dosage.

G-CSF administration

In each treatment, a blood examination was performed prior to treatment on the treatment day. Among the cases considered, there was no case in which administration of the drug was stopped due to adverse events other than hematotoxicity. Regarding hematotoxicity, G-CSF was administered in case of grade 1 adverse events, while it was withdrawn for a week in case of grade 2 or higher adverse events. The criteria for starting the administration of a G-CSF (Filgrastim) were to administer 150 μg by subcutaneous injection and postpone administration for one week in cases where grade 3 neutropenia was observed in the blood drawn after the first course was administered, namely right before the second course was administered. Also, administration was postponed for another week and 150 μg was administered in cases where the neutrophil count indicated grade 2 adverse events in the blood drawn before the second course was administered after the one-week postponement, and a total of 300 μg was administered over 2 straight days in principal in cases where the recovery of the neutrophil count was poor and a grade 3 or higher neutrophil count was observed. After the third cycle, the drug was administered from 4 to 7 days prior to the scheduled chemotherapy.

Cases

Four patients received adjuvant therapy during this period. Two cases were patients with sigmoid colon cancer (respectively stage IIIa, IIIb), one of the other cases was a patient with stage IIIa rectal cancer, and another was a patient with stage IIIb cancer of the transverse colon. In all cases, the treatment was completed in 12

cycles. There was no relapse during the therapy or after the end of the therapy. In the 3 cases other than the patient with cancer of the transverse colon, G-CSF was used for neutropenia regularly during the therapy according to the rule, as shown in the table. In 1 case, because neutropenia was observed on the due date of the second dosing, the use of G-CFS was immediately started, and its subsequent administration for 12 cycles was successfully completed. In the other 2 cases, beginning at the 5th and11th administration, respectively, G-CSF was administered prophylactically according to the rule of dosing. In 1 case, as neutropenia was not observed, administration for 12 cycles was completed without the use of G-CSF. In this case, the dosing interval was often more than 2 weeks for reasons related to the patient or clinic. The average dosing time is listed. Adverse effects other than neutropenia in these patients are listed. They were only grade 1 or 2 peripheral neuropathy, and no lesions that caused dose reduction or extension of the dosing period were observed except neutropenia. In addition, an intravenous access port was used in all cases.

Table 1:

	Age	Gender	Tumor	Stage	Completion	Recurrence	Term	GCSF	Delayed cycles
case 1 *	67	male	sigmoid	IIIA	yes	no	195 days	5, 6,7,8,9,10, 11,12	5, 6, 9, 10,
case 2 **	67	male	sigmoid	IV	yes	no	213 days	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12	3, 6, 7, 8, 9, 10
case 3	62	male	rectal	IIIA	yes	no	232 days	no	5, 8, 9, 11, 12
case 4	60	male	transverse	IIIB	yes	no	188 days	11, 12	7, 8, 11

Table 1 : * In case 1, at about the ninth cycle in case 1, the administration of G-CSF at 150 µg a week ahead did not bring about the recovery of neutrophils in the next week, so an additional administration of G-CSF at 150 µg was required; as a result the administration was delayed for two weeks. Since then, a week before the chemotherapy, the administration of G-CSF was performed for 2 straight days at a dose of 150 µg. ** In case 2, after the first chemotherapy, that is, before the second administration, blood analysis already showed neutropenia of grade 3, so the administration of G-CSF at 150 µg was performed one week in advance, but after the seventh administration, that is, just before the eighth administration, blood analysis showed neutropenia of grade 3 again. Since then, a week before the chemotherapy, the administration of G-CSF was performed for 2 straight days at a dose of 150 µg.
Completion: We defined the completion chemotherapy as Full administration of the planned dosage.

As for the length of time it took to administer the 12 courses, case 4 took 188 days and case 3 took 232 days, with the average of the 4 cases being 207 days. At about the ninth cycle in case 1, the administration of G-CSF at 150 µg a week ahead did not bring about the recovery of neutrophils in the next week, so an additional administration of G-CSF at 150 µg was required; as a result the administration was delayed for two weeks. Since then, a week before the chemotherapy, the administration of G-CSF was performed for 2 straight days at a dose of 150 µg. In case 2, after the first chemotherapy, that is, before the second administration, blood analysis already showed neutropenia of grade 3, so the administration of G-CSF at 150 µg was performed one week in advance, but after the seventh administration, that is, just before the eighth administration, blood analysis showed neutropenia of grade 3 again. Since then, a week before the chemotherapy, the administration of G-CSF was performed for 2 straight days at a dose of 150 µg. Because there was no neutropenia of grade 2 or more in case 3, G-CSF was not used. The delay of the administration occurred because of the patients' circumstances. In case 4, after the tenth administration, that is, before the eleventh administration, neutropenia of grade 3 was observed, so the administration of G-CSF at 150 µg was performed twice before the treatment.

DISCUSSION

We examined the adjuvant chemotherapy completion rates in a population of patients with stage III colon cancer to investigate the hypothesis that the same characteristics that predict differences in the initiation of adjuvant chemotherapy would predict the completion of a complete course of therapy. We identified the importance of the use of G-CSF in routine administration.

The impact of adjuvant therapy on cancer survival is one of our most important recent achievements in medical oncology. This milestone has been accomplished through the use of clinical trials, especially among patients with colon and breast cancer. The annual odds of death from breast cancer alone among patients in these trials has decreased by up to 28%, depending on the criteria used for patient enrollment, the types of treatment given, and the characteristics of the tumors themselves[1]. Similar, but less well-defined, results have been reported for colon cancer[2,7-9].

Progress has been made in the use of anticancer drugs by studying dosage and administration, through the co-administration of drugs with different action mechanisms or toxicity profiles, and by devising treatment schedules[10]. One of the characteristics of anticancer drugs is that, due to their toxicity, there is only a small difference between the drug amount needed to produce antitumor activity and the Maximum Tolerated Dose . For this reason , in clinical practice, situations occur in which sufficient efficacy is not obtained if the dose is reduced too readily. So the notion of "treatment intensity" has become important. In adjuvant therapy of breast cancer, it became clear that there was a difference in survival rates between a group given more than 85% of the scheduled amount of a drug and a group given less than that[11]. That is, it has become clear that the amount of a drug given per unit time is as important as the total treatment cycle or the gross drug amount given. This is likely because both concentrate-dose-dependent and time-dependent drugs were used in the regimen taken up in the present study. Meanwhile, with anticancer drugs, there exists the aforementioned Maximum Tolerated Dose, and the biggest factor that determines this dose is bone-marrow suppression. In our present report, it appears that bone-marrow suppression and neutropenia were avoided by our G-CSF dose method.

In the revised ASCO Guideline, the G-CSF administration of G-CSF with the intention to increase the dose intensity is not recommended[12]. However, chemotherapy aiming for the improvement of the antitumor effect by shortening the administration interval with the use of drug combinations instead of just increasing the dosage has attracted attention recent years. As some supporting data regarding this kind of chemotherapy have been obtained, its usability is also suggested in the ASCO Guideline, with the careful stipulation that the conduct of such chemotherapy should be limited only when it is confirmed with certainty by clinical studies or data. The correlation between the dosage of the antitumor agent and its treatment effects in malignant lymphoma and breast cancer has been suggested. In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF support is recommended in 2010 update of EORTC guidelines for the use of G-CSF[10]. Therefore, we examined the relationship between completion therapy and the treatment effects in the regimen for colorectal cancer.

In our study, we revealed that all four stage III colorectal cancer cases successfully completed 12 cycles of mFOLFOX6 adjuvant therapy with regular G-CSF administration. No dose reduction in the anticancer drug was revealed. The risk of cancer-related mortality was statistically significantly lower among those completing chemotherapy (relative risk = 0.79, 95% confidence interval = 0.69 to 0.89) than among those with no adjuvant therapy[13,14]. Also, it has been revealed that the rate of completion was 87% for an oxaliplatin and infusion fluorouracil/leucovorin (FOLFOX4) regimen[13,14] . It was concluded that the completion rate of the initial four cycles was as high as expected with manageable toxicity.

The importance of the completion of chemotherapy has been reported in adjuvant chemotherapy with 5-FU and doxorubicin after

D2-3 gastrectomy[15]. In this study, multivariate analysis demonstrated that the completion of chemotherapy is an independent prognostic factor of both disease-free and overall survival. However, dose intensity and relative dose intensity did not now show any effect on survival. In these studies, the G-CSF routine use of G-CSF for neutropenia was not described. Usually, the investigators reduced the dose following their protocol.

Our routine G-CSF administration for mFOLFOX6 adjuvant therapy clearly contributed to the completion of the therapy. Further investigation is needed to evaluate the usefulness of the completion of therapy in colon cancer adjuvant therapy.

REFERENCES

1. Laurie JA, Moertel CG, Fleming TR, Wieand HS, Leigh JE, Rubin J et al. Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. The North Central Cancer Treatment Group and the Mayo Clinic. J Clin Oncol 1989; 7:1447–56.
2. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990; 322:352–58.
3. Kanemitsu Y, Kato T, Shimizu Y, Inaba Y, Shimada Y, Nakamura K et al. A randomized phase II/III trial comparing hepatectomy followed by mFOLFOX6 with hepatectomy alone as treatment for liver metastasis from colorectal cancer: Japan Clinical Oncology Group Study JCOG0603. Jpn J Clin Oncol 2009; 39:406-9.
4. Dobie SA, Baldwin LM, Dominitz JA, Matthews B, Billingsley K, Barlow W . Completion of therapy by Medicare patients with stage III colon cancer. J Natl Cancer Inst 2006; 98:610-9.
5. Ozer H, Armitage JO, Bennett CL, Crawford J, Demetri GD, Pizzo PA,et al. American Society of Clinical Oncology.2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. J Clin Oncol. 2000; 18:3558-85.
6. Shimizu T, Satoh T, Tamura K, Ozaki T, Okamoto I, Fukuoka M, et al. Oxaliplatin/fluorouracil/leucovorin (FOLFOX4 and modified FOLFOX6) in patients with refractory or advanced colorectal cancer: post-approval Japanese population experience. Int J Clin Oncol 2007; 12:218-23.
7. Wolmark N, Rockette H, Fisher B, Wickerham DL, Redmond C, Fisher ER, et al . The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol 1993; 11:1879–87.
8. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM, et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Intern Med1995; 122:321–6.
9. Wolmark N, Rockette H, Mamounas EP, Jones J, Petrelli N, Atkins J. The relative efficacy of 5-FU+leucovorin (FU-LV), 5-FU+levamisole (FU-LEV) and 5-FU+leucovorin+levamisole (FU-LV-LEV) in patients with Ducke's B and C carcinoma of the colon: first report of NSABP C-04. ASCO proceeding1996; 15:205.
10. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, et al. European Organisation for Research and Treatment of Cancer.2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 2011; 47:8-32.
11. Ichinose I, Hamada Y, Mitsuyama S, Ishikawa E, Ikeda T, Kobayashi S, et al. Dose escalation study of epirubicin and docetaxel in patients with advanced or recurrent breast cancer. Chemotherapy 2008; 54: 379-85.
12. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006; 24:3187-205.
13. Jessup JM, McGinnis LS, Steele GD, Jr, Menck HR, Winchester DP. The National Cancer Data Base. Report on colon cancer. Cancer 1996; 78:918–26.
14. NIH Consensus Conference.: Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990; 264:1444–50,.
15. Jeung HC, Rha SY, Noh SH, Min JS, Kim BS, Chung HC.Adjuvant 5-fluorouracil plus doxorubicin in D2-3 resected gastric carcinoma: 15-year experience at a single institute. Cancer. 2001; 91:2016-25.