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Review Article

UNRESECTABLE COLORECTAL CANCER CASES RECIEVING NO-DOSE-REDUCTION FOLFIRI THERAPY WITH THE REGULAR ADMINISTRATION OF GRANULOCYTE COLONY-STIMULATING FACTOR SUPPORT: CASE REPORT WITH REVIEW OF LITERATURE

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ABSTRACT

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 RDI, and to review the use of G-CSF in standard chemotherapy for advanced colorectal cancer. Data were collected retrospectively on patients with colorectal cancer who had been treated with FOLFIRI. Two cases were patients with sigmoid colon cancer (both stage IV), and one of the other cases was a patient with stage IV rectal cancer. In all cases, the treatment was completed in 12 cycles. There was no relapse during the therapy nor after the end of the therapy. In RDI in the cases considered, 2 cases where G-CSF was administered displayed high values such as 94.5% and 95.8%, and CR was observed in the second case. Our routine G-CSF administration for FOLFIRI therapy clearly contributed to the RDI of the therapy. Further investigation is needed to evaluate the usefulness of the completion of therapy in colon cancer adjuvant therapy.

Keywords: FOLFIRI, G-CSF, Colorectal Cancer, RDI

INTRODUCTION

The role of chemotherapy in unresectable 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. FOLFIRI (a regimen infusion of l-leucovorin (LV) followed by a 5-FU bolus and infusion every 2 weeks, with irinotecan infusion) is the most common standard regimen for it[3].

Early studies suggested a link between chemotherapy dosing and outcomes not only in high-risk breast cancer, but also in colorectal cancer, pancreatic cancer, bile duct cancer, and so on. To help define the impact of relative dose intensity (RDI) and the role of growth factor support, we conducted a systematic review of our experiences. Many such cancer patients do not achieve the planned RDI. Older age, obesity and febrile neutropenia are associated with reduced RDI, which has led to worse survival in several studies, particularly those including anthracyclines. G-CSF prophylaxis improved RDI in most, but not all, studies. There may be a threshold above which increasing RDI does not further improve outcomes (~85% for CMF and anthracycline-based regimens). For lymphoma, there is strong evidence that patients benefit from full-dose chemotherapy, with RDI reductions associated with reduced survival. The definition of "full dose" is, however, unclear. Older age and higher disease stage may be associated with reduced RDI, and G-CSF improved the chances of higher RDI in most studies[4] .

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 recommended the use of G-CSFs as a secondary prophylaxis to protect against and prevent new episodes of febrile neutropenia; they also recommended dose modifications in cases 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 RDI, and to review the use of G-CSF in standard chemotherapy for advanced colorectal cancer.

MATERIALS AND METHODS

Study Design and Patient Selection

Data were collected retrospectively on three patients with colorectal cancer who had been treated between April 1 2010 and June 30 2011 with FOLFIRI (a regimen of a 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 irinotecan 180 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, and 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 of 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 the administration of the drug was stopped due to adverse events other than hematotoxicity. Regarding hematotoxicity, G-CSF was administered in cases with grade 1 adverse events, while it was withdrawn for a week in cases with 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 principle 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

Three patients received FOLFIRI therapy during this period(Table1). Two cases were patients with sigmoid colon cancer (both stage IV), and one of the other cases was a patient with stage IV rectal cancer. In all cases, the treatment was completed in 12 cycles. There was no relapse during the therapy nor after the end of the therapy. In RDI in the cases considered, 2 cases where G-CSF was administered displayed high values such as 94.5% and 95.8%, and CR was observed in the second case(Table1).

In all cases, the treatment was completed in 12 cycles. There was no relapse during the therapy nor after the end of the therapy (Table 1). In the second and third cases, G-CSF was used for neutropenia regularly during the therapy according to the rule, as shown in the table 1. In these 2 cases, because neutropenia was observed on the due date of the second dosing, the use of G-CSF was immediately started, and its subsequent administration for 12 cycles was successfully completed In the other case, as Grade 3 and 4 neutropenia was not observed, the administration of 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. These included 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.

In cases 2 and 3, 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 for 2 straight days at a dose of 150 μg. The delay of the administration occurred because of the patients' circumstances.

DISCUSSION

The impact of chemotherapy on cancer survival is one of the 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, thereis only a small difference between the drug amounts 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. 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[4]. 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, G-CSF administration with the intention to increase dose intensity is not recommended[11]. However, chemotherapy intending to improve the antitumor effect by shortening the administration interval with the use of drug combinations instead of just increasing the dosage has attracted attention in recent years. As some data supporting this kind of chemotherapy have been obtained, the ASCO Guideline suggests that this treatment may be used with the limitation that the conduct of such chemotherapy should be used only in instances in which it is confirmed with certainty by clinical studies or data. The correlation between the dosage of the antitumor agent and the treatment effects in malignant lymphoma and breast cancer has been suggested[4,5,11,12]. Therefore, we examined the relationship between RDI and treatment effects in the regimen for colon cancer.

There are two ways to enhance dose intensity; increase the amount of each dose without changing the dosing interval or shorten the dosing interval without changing the dosing amount[4,12]. Some report that this way is effective in breast cancer chemotherapy, but in experimental cases, the standard dosing amount and intervals were maintained, G-CSF was periodically used, and the therapeutic effect was good, so careful consideration must still be given when choosing the method of enhancing dose intensity[11,12]. Also, the way in which the dosing amount can be increased most is through transplantation, which can be supported by hematopoietic cells; however, the best way to increase the cure rate through high dose chemotherapy and transplantation has not yet been established in the field of solid tumors, except for testicular tumors. The dose intensity and antitumor effect are positively correlated in the relatively early period when the tumor is large and the disease has progressed, as in the present experimental cases. Therefore it is very important to maintain RDI in this period. Also, continued healing for a long period atrophies the whole tumor, which eventually contributes to the long-term control of the tumor. Thus, there is a close relationship between therapeutic effect, dose intensity, and total dosing amount. Therefore, in the method involving the adoption of a periodical dose of G-CSF in the early period, as in the present experimental cases, the dose amount is not decreased and the prolongation of dose intervals is also minimized (Table 1). This was considered to be a way to maintain excellent dose intensity. We should adjust conventionally used anticancer drugs to the patient's condition, maintain appropriate dose intensity and dose intervals, and refrain from decreasing the amount of drugs or prolonging the dose intervals for healing, especially in adjuvant therapy. Note that for some drugs the antitumor effect and toxicity cannot be explained only by dose intensity.

Table 1

Case	LV(RDI)	CPT11(RDI)	5-FU bolus(RDI)	5-FU infusion(RDI)	Ave.(RDI)	GCSF administration	Efficacy
1	83.6%	89.2%	90.6%	90.6%	88.5%	NA	SD
2	94.4%	93.5%	94.4%	95.5%	94.5%	150ugX2	SD
3	97.2%	92.5%	97.2%	96.1%	95.8%	150ugX2	CR
Ave.	91.7%	91.7%	94.1%	94.1%	92.6%		

In our study, we revealed that stage IV colorectal cancer cases successfully completed 12 cycles of FOLFIRI therapy with regular G-CSF administration (Table 1). High RDI and no dose reduction in the anticancer drug were 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]. Also, it has been revealed that the average RDI was 85% for the FOLFIRI regimen[14]. It was concluded that the completion rate of the initial four cycles was as high as expected with manageable toxicity.

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

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