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Managing anemia with epoetin alfa in patients with rectal cancer

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Background. *Anemia is one of the most challenging problems in clinical oncology due to its high prevalence among the patients with malignant diseases. The purposes of our study were: (1) to assess the potential of epoetin alfa therapy to prevent the decline in Hb concentrations that typically accompanies chemotherapy/radiotherapy (ChT/RT) of the patients with rectal cancer; (2) to test the hypothesis that the use of epoetin alfa significantly reduces the transfusion requirements in the patients with rectal cancer treated with ChT/RT after surgery, and (3) to evaluate the safety profile of the administration of epoetin alfa in the clinical setting.*

Methods. *Sixty patients who underwent surgery for rectal cancer were prospectively enrolled. Group A consisted of 39 patients with Hb concentrations ≤13 g/dl at the start of ChT/RT following surgery, and group B of 17 patients with Hb concentrations >13 g/dl at the start of ChT/RT following surgery, but whose Hb concentrations fell below 13 g/dl during the ChT/RT protocol. The starting dose of epoetin alfa in both groups was 10,000 IU subcutaneously (sc) three times a week (tiw). The following major parameters were evaluated: (1) change in Hb concentrations relative to the baseline as measured at 4-week intervals, (2) allogenic blood transfusion requirements in relation to Hb concentrations, and (3) incidence and severity of adverse events and their potential relationship to epoetin alfa administration.*

Results. *The study protocol was completed in 56/60 patients. In group A, a statistically significant increase in Hb concentration ($p<0.001$) was observed after the first 4 weeks of epoetin alfa treatment compared to the baseline values, with the mean increase of Hb concentration of 1.97 g/dl ± 0.91 g/dl and Hb concentrations remained significantly increased through the whole study ($p=0.0017$). In group B, a continuous decrease in Hb concentrations was observed during the first weeks of therapy, reaching the level of statistical significance after 3 weeks of postoperative treatment. After the initiation of epoetin alfa treatment, an increase of Hb concentrations and their maintenance at ≤12 g/dl was observed also in group B. Not a single patient enrolled in the study needed transfusion. None of described adverse events was connected to the epoetin alfa treatment.*

Conclusions. *The results of the present study show that epoetin alfa is safe and effective in maintaining Hb concentrations during the adjuvant therapy in rectal cancer patients. It significantly increases Hb concentrations and reduces transfusion requirements in the patients receiving chemoradiotherapy after surgery for rectal cancer.*

Key words: rectal neoplasms – radiotherapy – drug therapy; anemia – drug therapy; epoetin alfa

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Introduction

Anemia is one of the most challenging clinical problems in clinical oncology due to its high prevalence among the patients with malignant diseases.[1,2] It is now recognized as an independent prognostic factor for patient's survival[3-12] and can also have a considerable negative effect on patient's quality of life.[7,13-17]

Generally, clinical studies have shown that recombinant human erythropoietin (epoetin alfa) administered once weekly or three times a week improves hemoglobin (Hb) levels, decreases transfusion requirements,[1,4,7,12-20] improves quality of life,[14-17,21-24] and may also improve the survival in the patients with cancer-related anemia.[4,7,25-27] However, despite such efficient approach to the anemia management, a comprehensive survey[28] indicated that only 36% of patients with solid tumors who were anemic received treatment for their anemia. Moreover, treatment of anemia was initiated at lower Hb levels than recommended (mean Hb level of 9.6 g/dl for solid tumors).[28]

Accordingly, it is mandatory to assess the feasibility and safety of the administration of epoetin alfa in each individual type of cancer. The purposes of our study were: (1) to assess the potential of epoetin alfa therapy to prevent the decline in Hb value that typically accompanies chemotherapy/radiotherapy (ChT/RT) of the patients with rectal cancer; (2) to test the hypothesis that the use of epoetin alfa significantly reduces the transfusion requirements in the patients with rectal cancer treated with ChT/RT after surgery, and (3) to evaluate the safety profile of administration of epoetin alfa in the clinical setting.

Methods

Sixty patients who underwent rectal cancer surgery were prospectively enrolled in the study between March 2002 and December 2003 (Table 1). The following inclusion criteria were used:

- histologic confirmation of adenocarcinoma of the rectum (pathohistological stage II and III) that were amenable to postoperative ChT/RT;
- age above 18 years;
- WHO performance status 0-2;
- Hb level ≤13 g/dl;
- serum transferrin saturation (TSAT) >20%.

Exclusion criteria were: uncontrolled or severe cardiovascular disease, including recent (<6 months) myocardial infarction; uncontrolled hypertension (diastolic blood pressure >95 mm Hg); congestive heart failure; uncontrolled or unexplained seizures; major illness

Table 1. The study population

Group	N	Description	Mean age/Range (years)	Gender (male/female)
A	39	Hb level ≤ 13 g/dl at the start of the Cht/RT treatment following surgery; enrolled at the start of the Cht/RT	64.8±14	19 M/20 F
B	17	Hb level >13 g/dl at the start of Cht/RT treatment following surgery; enrolled during the Cht/RT	68.5±9.5	11M/6F
All	56	Patients with Hb≤13 g/dl treated for rectal cancer with Cht/RT after surgery	66.6±11.7	30 M/26 F

ChT/RT – chemo-radiotherapy; N – number of patients

or infection within the preceding month, history of thrombotic or other vascular events during the preceding 6 months; known hypersensitivity to epoetin alfa or one of its components; pregnancy, lactation, or inadequate method of contraception in females with childbearing potential.

Surgical procedures were as follows: abdominoperineal resection (APR; 23 patients), low anterior resection (LAR; 28 patients), anterior resection (RRA; 6 patients), Hartman's palliative resection (2 patients) and coloanal anastomosis (CA; 1 patient).

After surgery, all patients were treated on adjuvant setting at the Institute of Oncology in Ljubljana, Slovenia, following the protocol outlined below and approved by the Protocol Review Board and Committee for Medical Ethics at the Institute of Oncology. All patients were informed about the study protocol.

At the enrolment, baseline data (history, physical and laboratory tests) were collected in all patients, including complete blood cell count, reticulocyte count, levels of serum iron, folate and vitamin B12, transferin saturation (TSAT) and ferritin.

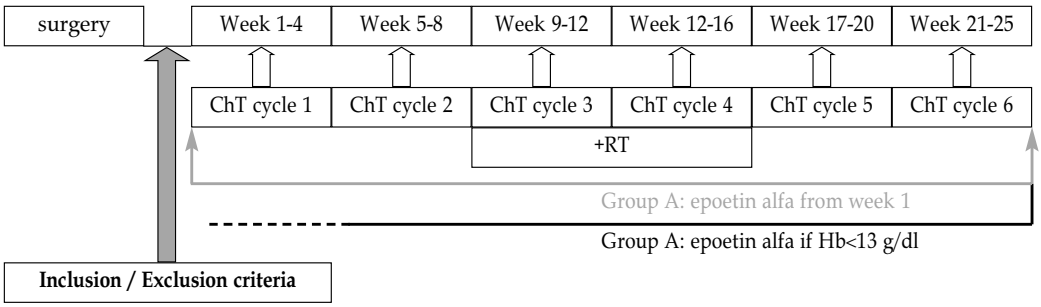
On the basis of Hb concentration, the patients were divided into two groups. Group A consisted of 39 patients with Hb level ≤13 g/dl at the start of the ChT/RT, and group B of 17 patients with Hb level >13 g/dl at the start of the ChT/RT following surgery, but whose Hb fell below 13 g/dl during the ChT/RT.

Chemo-radiotherapy protocol

The patients were treated following the combined ChT/RT protocol as shown in Figure 1. During 25 weeks, the patients received 6 cycles of chemotherapy with 5-fluorouracil (5-FU), 425 mg/m^2/day intravenously (iv), and Ca-folinat, 50 mg/day iv both during the days 1-5. Because of concomitant irradiation during the 4th cycle of ChT, the doses of 5-FU and Ca-folinat were reduced to 75% level for this cycle only. The cycles were repeated every 28 days. The patients were irradiated with 10-15 MV linear accelerator photon beams to a tumor dose of 50.4 Gy and daily fractions of 1.8 Gy, applied five-times/week.

Epoetin alfa administration protocol

In group A, the treatment with epoetin alfa started on day 1 of ChT/RT, whereas in group B, epoetin alfa was administered during the course of ChT/RT when a patient's Hb concentration decreased below 13 g/dl. The starting dose of epoetin alfa was 10,000 IU subcutaneously (sc) three times a week (tiw). Hb concentration was monitored regularly at monthly intervals during chemotherapy and weekly during ChT/RT. If the Hb concentration increased by less than 1 g/dl from the baseline after 4 weeks of initiating epoetin alfa, the dose of the drug was increased to 20,000 IU sc tiw. In case of the increase of Hb concentration by more than 2 g/dl per month, the dose of epoetin alfa was reduced to 10.000 IU biw.



ChT cycle: Chemotherapy cycle; RT: Radiotherapy

Figure 1. Protocol of the study

The administration of epoetin alfa was interrupted when Hb concentration increased above 14 g/dl and was initiated again when it fell below 12 g/dl at a dose of 10.000 IU twice a week (biw).

The application of epoetin alfa was abolished if the treatment with epoetin alfa was not effective (no expected rise in Hb level after dose escalation) or in cases of developing a severe adverse reaction related to epoetin alfa.[29]

All patients included in the study would be transfused if Hb concentration was <10 g/dl.

Iron treatment, transfusion requirements and concomitant therapy

The patient's iron status, including transferrin saturation-TSAT (serum iron/iron binding capacity x 100; %) and serum ferritin (μg/L) was evaluated on weekly basis during ChT/RT, and on monthly basis during ChT. To avoid iron depletion of available stores and to support adequately erythropoiesis, stimulated by epoetin alfa, the patients with TSAT <20% and/or serum ferritin <100 μg/L required supplemental iron (300 mg elemental iron orally per day).

Follow up

In the postoperative phase, the patients were followed on weekly basis for a total of 25 weeks. Safety evaluations were carried out by clinical laboratory tests and by assessing the incidence and severity of treatment-related side effects.

Statistical analysis

The following parameters were evaluated: (1) change in Hb concentration relative to the baseline as measured at 4-week intervals, (2) blood transfusion requirements in relation to Hb level, and (3) incidence and severity of adverse events and their potential relationship to epoetin alfa administration. Hb concentration was presented as mean ± standard deviation (SD). Statistical analysis was performed using the two-sided paired t-test. A probability value of <0.05 was considered statistically significant.

Results

The study protocol was completed in fifty-six of sixty patients (56/60; 93.3%). The remaining four patients (4/60; 6.7%) included in the study were not included in statistical evaluations due to insufficient data. Forty-five of fifty-six patients (45/56; 80.3%) completed all six cycles of chemotherapy and radiation therapy as specified in the protocol. Eleven patients (11/56; 19.7%) received less than six cycles of ChT (5 cycles- 3 patients; 4 cycles- 5 patients; 2 cycles- 3 patients) due to the appearance of adverse events (ileus, dehydration, nausea, leucopoenia, febrile neutropoenia, infection, cardial decompensation, radioproctitis, mucositis).

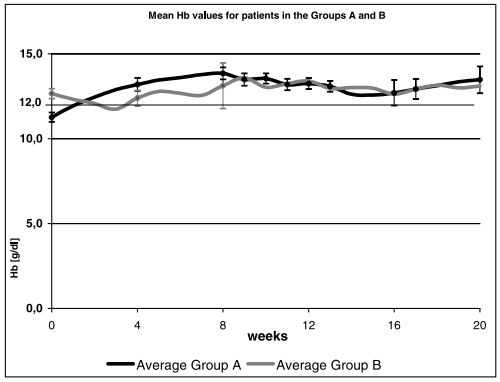


Figure 2. Mean hemoglobin (Hb) concentrations in the patients treated with epoetin alfa in groups A and B. In group A, Hb levels were statistically increased from the enrolment in the study onwards. In group B, an initial decrease in Hb concentrations (weeks 0 through 3) was observed. After the initiation of the treatment with epoetin alfa, mean Hb concentrations in group B also reached the level of 12 g/dl till the end of the treatment.

Hematological response

In group A, a statistically significant increase in Hb concentration ($p<0.001$) was observed after the first 4 weeks of epoetin alfa treatment compared to the baseline values, with the mean increase of Hb concentration of 1.97 g/dl ± 0.91 g/dl. As shown in Figure 2, Hb concentrations remained significantly increased from the initial values through the rest of the treatment ($p=0.0017$). In group B, a continuous decrease in Hb concentrations was observed during the first weeks of the therapy, reaching the level of statistical significance after 3 weeks of postoperative treatment, ($p=0.006$). After the initiation of epoetin alfa treatment, an increase of Hb concentrations (on average 0.7 g/dl ± 0.4 g/dl/4 weeks) and their maintenance at ≥12 g/dl were observed (Figure 2).

Figure 3 illustrates the frequency of Hb readings <13 g/dl in the patients from group A compared with those from group B during RT part of the protocol. In group A, a progressively smaller share of patients with Hb values <13 g/dl was registered during RT. None of the patients had Hb concentrations <13 g/dl at the 6th week of the irradiation. On the other hand, in group B, the share of patients with Hb concentrations <13 g/dl progressively increased during RT. In this subgroup, epoetin alfa was typically initiated during the 3rd week of RT.

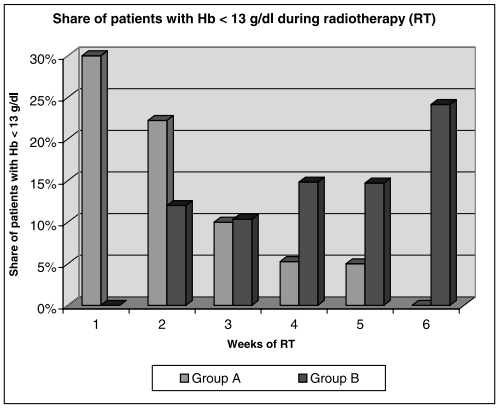


Figure 3. Prevalence of patients with hemoglobin (Hb) concentration <13 g/dl during the RT part of the protocol. In group A, a progressively smaller share of patients with Hb concentrations <13 g/dl during RT was observed and with none of the patients with Hb values 13 g/dl at the end of RT. In group B, the share of patients with Hb concentration <13 g/dl progressively increased during RT.

Transfusion requirements

Not a single patient enrolled in the study needed transfusion.

Safety and tolerability of epoetin alfa

Nine adverse events that occurred in 6 patients who completed the study were recorded: ileus, dehydration, nausea, leucopoenia, febrile neutropoenia, infection, cardial decompensation, radioproctitis, and mucositis. None of the described adverse events was connected to the epoetin alfa treatment.

Discussion

In the present study, we tested the efficacy and feasibility of epoetin alfa administration in the patients receiving chemo-radiotherapy after surgery for rectal cancer. Our results demonstrate that, also in the patients with this type of cancer, epoetin alfa effectively increases and maintains Hb concentration during ChT/RT at the clinically requested level. None of the patients enrolled in our study required transfusion despite the aggressiveness of the treatment protocol.

The results of our study corroborate the findings of randomized controlled trials with epoetin alfa in the treatment of anemia in other solid and hematological malignancies. These studies have consistently shown an increase in Hb concentrations, a decrease in transfusion requirements, and an improvement in patient's energy level, their ability to maintain daily activities, and their overall quality of life.[1,4,7,13-19,21-24]

Our results also confirmed an excellent safety profile of epoetin alfa. Although

thrombotic/vascular events and hypertension have been reported previously in the patients treated with epoetin alfa,[27] no such events were observed in our population of patients.

Recent studies on ovarian and lung cancer patients receiving cisplatin-based chemotherapy have demonstrated that higher Hb concentrations exerted a positive effect on patient's tolerability of chemotherapy.[30-32] The patients with low Hb-concentrations due to either the disease itself or myelotoxicity of chemotherapy had a lower capacity to compensate for treatment toxicity.[30]

In addition, our results indicate that the epoetin alfa treatment is particularly beneficial in combined treatment protocols. The major challenge remains how to identify the patients who would most likely develop anemia during the combined therapy and who are candidates for prophylactic epoetin alfa treatment. The benefits of epoetin alfa prophylaxis in the context of current clinical guidelines, which recommend starting with epoetin therapy at the Hb concentration range of 10-11 g/dl,[33,34] are yet to be defined.

Anemia is a major cause of fatigue which is clinically manifested in 40-80% of patients with malignancies[15,20,35-37] and usually critically influences the quality of their lives. Indeed, fatigue is at least as common among the most reported bothersome symptoms in the patients with cancer as the pain is.[13,15,17] On the other hand, many authors have reported that the problem of cancer-related fatigue is frequently not assessed adequately because it is not mentioned by patients, assessed by physicians, or not addressed to as an integral part of the treatment evaluation protocols.[38] Obviously, it is of critical importance to identify the fatigue in each individual patient and to offer him appropriate therapeutic option to alleviate it.

Hypoxia in the tumor has been recognized as a key regulator of tumor growth. Sustained hypoxic environment in a growing tumor may trigger changes that can result in a more aggressive phenotype of tumor cells.[39-41] Many studies have demonstrated a reduced probability of local control and worse survival results in the patients with hypoxic tumors, treated with ChT and/or RT.[42] In case of RT, the reduction in radiosensitivity of tumor cells should be seriously considered when the oxygen partial pressure in a tumor decreases below 25-30 mmHg. In general, a two- to threefold higher radiation dose is required to kill completely the hypoxic cells, compared with well-oxygenated cells, a difference referred to as the oxygen enhancement effect.[43] The increase in Hb concentrations, which improves the oxygen-carrying capacity of blood, is also correlated with better response to chemotherapy.[44]

To conclude, the results of the present study show that epoetin alfa is safe and effective in maintaining Hb concentrations during the adjuvant therapy of rectal cancer patients. It significantly increases Hb concentrations and reduces transfusion requirements in the patients receiving chemoradiotherapy after surgery for rectal cancer.

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