Anemia may influence the outcome of patients undergoing neo-adjuvant treatment of rectal cancer

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Background: We hypothesized that anemia could represent one of the major factors influencing the outcome of patients undergoing neo-adjuvant treatment of rectal cancer.

Patients and methods: This analysis included all the consecutive patients who underwent neo-adjuvant treatment (chemotherapy and/or radiotherapy) before surgery for rectal cancer in three oncology/radiotherapy departments from June 1996 to December 2003.

Results: Three hundred and seventeen patients were eligible for our analysis. Median age at diagnosis was 64 years (range 26–88 years); male/female ratio was 184/133. Two hundred and eighty-five patients (89.9%) were diagnosed with adenocarcinoma, while 32/317 (10.1%) with mucinous adenocarcinoma. Neo-adjuvant treatments carried out were as follows: radiotherapy alone in 75/317 patients (23.7%), radiotherapy plus chemotherapy in 242/317 patients (76.3%). At univariate and multivariate analysis, only the hemoglobin (Hb) level (group 1: ≤12 g/dl versus group 2: >12 g/dl) resulted in a significant factor for disease-free survival. The role of the Hb level seemed to be confirmed further by the clinical downstaging obtained in 55% of patients in group 2, in comparison with 35% of the patients achieving a significant downstaging in group 1.

Conclusion: Our results indicated that anemia could represent an important parameter able to influence the outcome in patients receiving neo-adjuvant treatment of rectal cancer.

Key words: rectal cancer, anemia, prognostic factors

Background

Anemia is common in cancer patients, especially among those receiving myelosuppressive chemotherapy and radiotherapy. The relationship between hemoglobin (Hb) levels and health-related quality of life is well known and justifies the correction of anemia in clinical practice.

On the other hand, correction of anemia by blood transfusions may be dangerous, not only by increasing the risk of infections and hemolytic reactions but also because they seem to cause an immunodepression determined by lymphocytes interfering with the outcome of cancer treatments [1].

In fact, anemia is a proved predictive factor for radiosensitivity. Schwartz [2] showed that hypoxia reduces the radiosensitivity of cells and Hollaendre et al. [3] defined the necessity to increase dose radiation in hypoxegenated tissues. The outcomes following curative-intent radiation therapy are adversely influenced by poor i.t. oxygenation and the presence of anemia [4–6]. Recently, Harrison et al. [7] showed that i.t. hypoxia may directly contribute to genomic instability and mutagenesis.

Since most cancers may benefit from a combination of chemotherapy and radiotherapy, anemia may represent a crucial factor in order to obtain favorable clinical results in these patients. The analysis of the relationship between anemia and outcome in several tumors seems to support this hypothesis.

A Canadian retrospective experience noticed that a higher average weekly nadir Hb correlated with a better overall survival (OS) rate in patients affected by cervical cancer undergoing radiation treatment [8]. Obermeyer et al. [9] confirmed that the nadir Hb level is a prognostic relevant factor predicting the clinical response to chemoradiation in cervical cancer patients receiving chemoradiation.

Similar results were found in head and neck cancer patients. Different studies conducted in patients with these tumors have revealed Hb level as a powerful prognostic factor for locoregional tumor control [10–15], disease-free survival (DFS) [16] and OS [10, 12, 13, 15]. Recently, anemia has been introduced as a factor of a prognostic index score in metastatic nasopharyngeal carcinoma [17]. Furthermore, Wagner et al.
Anemia has been demonstrated to be a predictive indicator of response to chemoradiotherapy in several solid tumors.

**results**

Three hundred and seventeen patients with rectal cancer received neo-adjuvant concomitant chemoradiotherapy. Table 1 summarizes the patients’ characteristics. Seventy-five (23.7%) patients received radiotherapy alone and 242 (76.3%) patients received concomitant chemoradiotherapy. Chemotherapy consisted of fluoropyrimidines alone in 149 patients (47%) and fluoropyrimidines in combination with other agents (cisplatin, oxaliplatin or mitomycin C) in 93 (29.3%) patients. The majority of patients (60.3%) underwent anterior resection of rectum. Miles was necessary in 81 patients (25.9%) and proctocolectomy in 22 patients (7%). All the patients underwent surgical resection with surgical margins >1 cm. Local recurrences were observed in 53 patients (16.7%) while distant metastasis appeared in 25 out of the above-mentioned 53 cases.

Pretreatment Hb level ranged from 7.9 to 17.9 g/dl (median 14.05 g/dl). Only one patient had Hb <8 g/dl during the treatment and he was given a blood transfusion. Erythropoietic growth factors were used in only one patient. We recorded a decrease of the Hb level after treatment completion in 179 patients.

When considering DFS, there was a significant difference in subgroups of patients with lower levels of Hb. In particular, DFS was worse in patients with Hb ≤12 g/dl (group 1) versus Hb >12 g/dl (group 2, $P=0.0183$) (Figure 1).

The role of the Hb level seemed to be confirmed further by the clinical downstaging obtained in ~55% of patients in group 2, in comparison with 35% of the patients achieving a significant downstaging in group 1 ($P=0.05$).

At univariate and multivariate analysis, including the following characteristics: age, sex, histology, type of surgery, neo-adjuvant treatment and Hb level, only the Hb level (group 1: ≤12 g/dl versus group 2: >12 g/dl) resulted in a significant factor for DFS (Table 2).

No significant differences in the overall patient survival were observed on the basis of the Hb level, even if a trend of survival benefit was present in the group of patients with a better Hb level ($P=0.097$). The relatively short follow-up could justify the absence of a significant difference.

**conclusions**

Anemia has been demonstrated to be a predictive indicator of response to chemoradiotherapy in several solid tumors.
Our results seem to show that, even in rectal cancer patients receiving neo-adjuvant chemoradiotherapy, anemia is able to predict clinical response to treatment.

According with our findings, several studies indicated a defined role of pretreatment Hb value. However, most of these data come from retrospective analyses and other trials did not confirm these results. MacRae et al. [20] demonstrated that presenting Hb, average Hb and minimum Hb level during therapy were not statistically significant predictive of survival in NSCLC patients, while declining Hb during chemoradiotherapy had a significant improvement on OS. A decrease of Hb level from 13.8 to 12.8 g/dl resulted in a 6% decrease in locoregional tumor control (P = 0.006) in early larynx cancer patients. In other groups of head and neck cancer patients, the post-treatment Hb value correlated with DFS [14].

In fact, by dividing our patients in two groups according to patients’ Hb level (group 1: £ 12 g/dl; group 2: >12 g/dl), we found that the tumor clinical downstaging was better in group 2, emphasizing the already known role of anemia as predictive factor for radiosensitivity. Furthermore, we observed a better DFS in non-anemic patients, indicating that anemia can be considered a prognostic factor in patients undergoing neo-adjuvant treatment with curative intent for rectal cancer. Box et al. [24] has recently analyzed a series of 100 patients with rectal cancer and found similar results: non-anemic patients achieved better tumor response and experienced less local recurrence (7% versus 38% P = 0.003) than anemic patients. Also the 2-year survival rate was improved in non-anemic patients (91% versus 64%, P = 0.021). Although we found a significant difference in DFS between patients who presented anemic or did not, the difference we observed in OS did not confirm these results. MacRae et al. [20] demonstrated that presenting Hb, average Hb and minimum Hb level during therapy were not statistically significant predictive of survival in NSCLC patients, while declining Hb during chemoradiotherapy had a significant improvement on OS. A decrease of Hb level from 13.8 to 12.8 g/dl resulted in a 6% decrease in locoregional tumor control (P = 0.006) in early larynx cancer patients. In other groups of head and neck cancer patients, the post-treatment Hb value correlated with DFS [14].

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reach the statistical significance. This did not surprise us, since median follow-up of our sample is too short to show significant difference. In fact, given that most rectal cancers relapse within 1 year, the number of events was sufficient to detect a difference in DFS, while we probably need a longer follow-up to reveal an improvement in OS especially in non-anemic patients.

Despite the association between anemia and poor prognosis in patients who are treated with chemoradiotherapy for solid tumors, there is no clear evidence whether anemia exerts an independent prognostic impact or whether anemia represents only an epiphenomenon indicating that anemia is linked to adverse prognostic factors such as large volume tumors. However, in a recent study, where the relationship between pretreatment anemia and survival was investigated in surgically treated patients with gastric cancer, the 10-year survival rate was better in non-anemic patients, but this difference was statistically significant only for tumors at I and II stages, where other likely prognostic factors were less influential on the outcome [25]. Moreover, it is unclear how far the correction of the anemia might have impact on prognosis. Since the use of erythropoietic agents has shown to improve survival in cancer patients, the correction of anemia should be considered for patients presenting with low Hb levels. This is supported by a retrospective study which looked at the comparison among patients with Hb >14.5 g/dl, patients with Hb <14.5 g/dl and patients with Hb <14.5 g/dl who were given erythropoietin alpha. Anemic patients had the worst outcome, but there was no difference between patients who started with a normal Hb value and those who were initially anemic but received erythropoietic growth factors [26].

In conclusion, although further investigations are needed, pretreatment anemia seems to be a prognostic factor for rectal cancer patients undergoing neo-adjuvant chemoradiotherapy and, since this is a modifiable factor, the correction of anemia could be advisable. These results prompted us to investigate two different approaches. The first one is to correct anemia earlier by the use of epoetin. Alternatively, we are assessing the effect of anemia on tumor hypoxia and on the alterations of genes involved in the hypoxia (HIF, CRC-1, VEGF) that may be responsible for a more aggressive behavior of tumors, in order to develop more effective adjuvant therapies by using novel agents able to inhibit the expression of the genes (VEGF; COX2; HIF inhibitors).

references