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CLINICAL INVESTIGATION **Esophagus**

EPOETIN ALFA IMPROVES SURVIVAL AFTER CHEMORADIATION FOR STAGE III ESOPHAGEAL CANCER: FINAL RESULTS OF A PROSPECTIVE OBSERVATIONAL STUDY

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Purpose: This prospective, nonrandomized study evaluates the effectiveness of epoetin alfa to maintain the hemoglobin levels at 12 to14 g/dL (optimal range for tumor oxygenation) during chemoradiation for Stage III esophageal cancer and its impact on overall survival (OS), metastatic-free survival (MFS), and locoregional control (LC).

Methods and Materials: Ninety-six patients were included. Forty-two patients received epoetin alfa (150 IU/kg, 3 times a week) during radiotherapy, which was started at hemoglobin less than 13 g/dL and stopped at 14 g/dL or higher. Hemoglobin levels were measured weekly during RT.

Results: Both groups were balanced for age, sex, performance status, tumor length/location, histology, grading, T-stage/N-stage, chemotherapy, treatment schedule, and hemoglobin before RT. Median change of hemoglobin was +0.3 g/dL/wk with epoetin alfa and −0.5 g/dL/wk without epoetin alfa. At least 60% of hemoglobin levels were 12 to 14 g/dL in 64% and 17% of the patients, respectively ($p < 0.001$). Patients who received epoetin alfa had better OS (32% vs. 8% at 2 years, $p = 0.009$) and LC (67% vs. 15% at 2 years, $p = 0.001$). MFS was not significantly different (42% vs. 18% at 2 years, $p = 0.09$).

Conclusions: The findings suggest that epoetin alfa when used to maintain the hemoglobin levels at 12 to 14 g/dL can improve OS and LC of Stage III esophageal cancer patients. © 2006 Elsevier Inc.

Esophageal cancer, Chemoradiation, Epoetin alfa, Locoregional control, Survival.

INTRODUCTION

Esophageal cancer carries a poor prognosis, with 41% 1-year, disease-specific survival in patients with Stage III disease (1). Considerable controversy exists regarding the optimal treatment, especially for locally advanced esophageal tumors with lymph node involvement. Prognostic factors are very important, as they can help to select the appropriate treatment for the individual patients. Various potential prognostic factors for esophageal cancer have been reported, such as age, performance status, tumor length, T-stage, N-stage, UICC-stage, and the hemoglobin level before radiotherapy (RT) (2–7). The prognostic impact of the hemoglobin level during RT on treatment outcome has also been described for endometrial carcinoma and cervix cancer (8, 9). The hemoglobin level is associated with tumor oxygenation, which plays an important role with respect to the treatment effect of irradiation. Radiobiological data suggest tumor hypoxia to be associated with an increased resistance to radiation-induced tumor cell kill because lower production of cytotoxic free radicals results in less DNA damage (10). Thus, tumor hypoxia results in a worse treatment outcome. Tumor oxygenation can be affected by the oxygen-carrying capacity of the blood, which is represented by the hemoglobin level. Tumor oxygenation can be reduced by anemia. Contrary to intuition, an excessively high hemoglobin level is also associated with a drop in nutritive perfusion because of an increase in viscous resistance to flow that decreases tumor oxygenation. The Danish Head and Neck Cancer Study (DAHANCA) demonstrated that the hemoglobin level has to be considered an important prognostic parameter for treatment outcome in head-and-

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neck cancer patients and that hemoglobin levels higher than the normal range had a negative impact on outcome (11, 12).

Hemoglobin levels of 12 to 14 g/dL appear optimal for tumor oxygenation (13). Thus, the patients' prognosis may be improved by maintenance of the hemoglobin levels within this optimal range.

A decrease of the hemoglobin levels during RT below 12 g/dL may be improved by the administration of recombinant human erythropoietin (14). Whether the effect of erythropoietin on the hemoglobin levels is associated with an improvement of tumor control and patient survival is controversial. Some reports, including our preliminary data, suggested a beneficial effect for erythropoietin with respect to outcome (15–19), whereas a prospective study from Germany in head-and-neck cancer patients suggested a poorer outcome for patients who received erythropoietin (20). However, that study has been criticized because of methodologic problems, which may have confounded the results. Many patients of the treatment group had hemoglobin levels greater than 14 g/dL during RT, which may have resulted in lower tumor oxygenation and, thus, a poorer prognosis. The patients of the control group had more favorable hemoglobin levels during RT than did the patients of the treatment group.

The administration of erythropoietin should be stopped if a hemoglobin level of 14 g/dL is reached, as has been done in our study (on-and-off administration when indicated). Thus, the potential effect of properly administered erythropoietin on treatment outcome in cancer patients still needs to be clarified.

Our prospective study evaluates the impact of on-and-off administration of epoetin alfa (ERYPO 10000;Janssen-Cilag, Neuss, Germany) during radiochemotherapy (RCT) on overall survival, metastatic-free survival, and locoregional control in Stage III esophageal cancer patients. Our preliminary report suggested that the administration of epoetin alfa was associated with significantly better locoregional control (18). The major goal of the study presented here was to evaluate whether the administration of epoetin may also improve overall survival.

METHODS AND MATERIALS

Ninety-six patients, 27 females and 69 males, who were treated with RCT for Stage III esophageal cancer between January 2001 and August 2005, were included in this prospective, nonrandomized study. Forty-three patients (45%) had T3N1M0 tumors, 14 patients (15%) had T4N0M0 tumors, and 39 patients (41%) had T4N1M0 tumors. The major goals of this prospective observational study were to evaluate the effectiveness of epoetin alfa in maintaining the hemoglobin levels at 12 to 14 g/dL (optimal range for tumor oxygenation) and to determine whether the administration of epoetin alfa can improve locoregional control and overall survival during RCT for Stage III esophageal cancer. Further endpoints investigated in this study were the impact of the administration of epoetin alfa on metastatic-free survival and on the median weekly change of hemoglobin levels during RCT.

Forty-two patients had received recombinant human erythropoietin (epoetin alfa) after informed consent to avoid hemoglobin levels less than 12 g/dL during radiotherapy. Fifty-four patients did not receive epoetin alfa. This control group was composed of patients who received chemotherapy in other institutions or who refused administration of epoetin alfa. The trial was performed after approval by the local ethics committee.

Blood transfusions were given if the hemoglobin level fell below 9 g/dL. Five patients with epoetin alfa and 9 patients without epoetin alfa received 2 to 4 transfusions during RCT.

Epoetin alfa in isotonic NaCl solution was administered s.c. (150 IU/kg) 3 times per week. Epoetin alfa treatment was started after the hemoglobin level became less than 13 g/dL, and epoetin alfa administration was stopped after the hemoglobin level reached 14 g/dL. Iron was administered orally (200 to 300 mg/day) if the ferritin was below 100 ng/mL or if the ferritin saturation was below 20%.

Radiotherapy was delivered by administration of 6-MV to 16-MV photons, with a daily dose of 1.8 Gy or 2.0 Gy, 5 days per week. Total radiation dose was 45 Gy to 50.4 Gy in 27 patients and 59.4 to 66 Gy in 69 patients. Nineteen patients were treated with 45 to 50.4 Gy plus surgery, and 8 patients were treated with 50 to 50.4 Gy alone. The initial RT fields (up to a dose of 50 to 50.4 Gy) had superior and inferior margins of 5 cm beyond the primary gross tumor volume. The lateral, anterior, and posterior margins were a minimum of 2 cm beyond the primary gross-tumor volume. Regional lymph nodes were included. After irradiation of the initial fields, a boost dose (9 to 16 Gy) was delivered to the primary tumor, with 2-cm margins, and to enlarged lymph nodes, with a minimum margin of 1 cm.

Chemotherapy with 5-FU (1,000 mg/m^2/day) was administered as a continuous infusion for 120 hours (Days 1 to 5 of each course) every fourth week. Cisplatin, at 75 mg/m^2, was administered as an i.v. bolus over 60 min on Day 1 of each course. The standard regimen was the administration of 2 chemotherapy courses concurrently with RT. In case of a large waiting list for the patients, 1 to 2 additional courses was administered before RT. In case of severe chemotherapy-related toxicity with the first course, a second course of chemotherapy was omitted.

Surgery for tumors of the upper third ($n = 3$) and middle third ($n = 9$) of the esophagus was performed with radical en-bloc resection of the esophagus and 2-field lymphadenectomy. The main parts of the 3 upper-third tumors were situated close to the middle third and did not involve the cervical esophagus, which allowed the application of surgery. For tumors of the lower third ($n = 7$), a transhiatal esophagectomy was performed. Esophageal continuity was restored by gastric tube. Preferentially, the route via the posterior mediastinum was taken.

The following potential prognostic factors were investigated with respect to OS, MFS, and LC: age ($\leq$60 years vs. $>$60 years), Eastern Cooperative Oncology Group (ECOG) performance status (1 vs. 2 to 3), tumor length ($<$7 cm vs. $\geq$7 cm, according to endoscopy), histology (squamous cell carcinoma [= SCC] vs. adenocarcinoma), histologic grade (G1 to G2 vs. G3), T-stage (T3 vs. T4, according to endoscopic ultrasound and computed tomography), N-Stage (N0 vs. N+ , according to endoscopic ultrasound and computed tomography), chemotherapy courses (1 course vs. 2 to 3 courses), treatment approach (45 to 50.4 Gy plus surgery vs. 50 to 50.4 Gy alone vs. 59.5 to 66 Gy alone), hemoglobin before RT ($<$12 g/dL vs. 12 to 14 g/dL and $>$14 g/dL), and application of epoetin alfa during RT (yes vs. no).

The hemoglobin levels were monitored weekly during therapy. Both treatment groups (patients who received epoetin alfa vs.