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CLINICAL INVESTIGATION **Head and Neck**

PRETREATMENT ANEMIA IS CORRELATED WITH THE REDUCED EFFECTIVENESS OF RADIATION AND CONCURRENT CHEMOTHERAPY IN ADVANCED HEAD AND NECK CANCER

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Purpose: Pretreatment anemia is an adverse prognostic variable in squamous cell head-and-neck cancer (HNC) patients treated with radiotherapy (RT) alone. Tumor hypoxia is an adverse parameter for treatment with RT alone or with RT and concurrent chemotherapy (CCT). Tumor hypoxia is more prevalent in patients who present with pretreatment hemoglobin (Hgb) concentrations less than 13 g/dL. RT/CCT improves survival over RT alone in advanced HNC, and its use is becoming more widespread. This study was performed to evaluate whether pretreatment Hgb less than 13 g/dL was correlated with treatment outcome in patients with advanced HNC treated with a uniform regimen of RT/CCT.

Methods and Materials: The study population consisted of patients with AJCC Stage III or IV, M0 HNC who were treated with 70 to 72.5 Gy accelerated hyperfractionated RT (1.25 Gy b.i.d.) and CCT consisting of 2 cycles of CDDP (12–20 mg/m^2/d × 5 days) and continuous infusion 5-FU (600 mg/m^2/d × 5 days) during Week 1 and Week 6. A planned break in RT occurred during Week 4. These patients were enrolled on the experimental arm of a prospective randomized trial that compared this regimen to hyperfractionated irradiation alone from 1990 to 1996. RT/CCT was delivered as standard therapy from 1996 to 2000. The primary endpoint was failure-free survival (FFS). Secondary endpoints included local-regional control and overall survival.

Results: One hundred and fifty-nine patients were treated from 1990 to 2000. The median (25–75%) pretreatment Hgb was 13.6 (12.2–13.5) g/dL. Hgb was 13 g/dL or higher in 105 patients and less than 13 g/dL in 54 patients. Primary tumor sites included oropharynx (43%), hypopharynx/larynx (36%), oral cavity (9%), and nasopharynx (6%). Seventy-eight percent of the patients with Hgb 13 g/dL or higher and 92% of the patients with Hgb less than 13 g/dL had a primary tumor stage of T3 or T4 ($p = 0.01$). Node-positive disease was present in 74 of 105 (70%) of patients with Hgb 13 g/dL or higher patients and in 36/54 (67%) of patients with Hgb less than 13 g/dL patients. Median follow-up of surviving patients was 42 months (range, 4–128 months). Five-year FFS was 75% for patients with Hgb 13 g/dL or higher vs. 50% for patients with Hgb less than 13 g/dL had a ($p < 0.01$). A total of 49 failures occurred in both patient cohorts. The median (25–75%) decrease in Hgb during RT/CCT was 2.2 (1.3–3.1) g/dL, both in patients who failed and in those who remained disease-free.

Conclusion: Pretreatment Hgb less than 13 g/dL is correlated with adverse outcomes in advanced HNC patients treated with RT/CCT. Whether anemia actually causes poor outcomes remains unknown. The therapeutic effect of anemia correction is being evaluated in prospective trials. © 2005 Elsevier Inc.

Head-and-neck cancer, Anemia, Radiotherapy, Combined-modality therapy, Hyperfractionation.

INTRODUCTION

Anemia adversely influences the prognosis of patients treated with radiotherapy (RT) alone for head-and-neck cancer (HNC) (1–6). The correlation between anemia and outcome for patients treated with radiation therapy and concurrent chemotherapy (RT/CCT) is unknown, however. Both a recent meta-analysis and several subsequent large randomized trials have demonstrated the superiority of RT/CCT over RT alone in patients with advanced HNC with respect to local-regional control, disease-free survival, and overall survival. RT/CCT is rapidly becoming the standard of care for the nonsurgical management of locally advanced disease (2, 7–11).

Radiation therapy and concurrent chemotherapy was initially used at our institution in 1990 and has been delivered in a relatively uniform fashion since then. The purpose of this analysis was to investigate the relationship between pretreatment Hgb concentration and treatment outcome for this group of patients.

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METHODS AND MATERIALS

Patient population and eligibility criteria

The medical records of all patients with locally advanced (American Joint Committee on Cancer [AJCC] Stage III or IV, M0) HNC treated with accelerated hyperfractionated RT and CCT in the Duke University Health System between 1990 and 2000 were reviewed. Those treated through 1996 participated in a prospective randomized trial of hyperfractionated RT with or without CCT, which has been previously reported (2). The remainder were treated RT/CCT delivered as standard therapy.

For the purpose of this study, eligible patients were classified as either anemic (Hgb $<$13 g/dL) or nonanemic (Hgb $\geq$13 g/dL) on the basis of their pretreatment Hgb level. This cutoff was chosen on the basis of previous studies at our institution that demonstrated a higher rate of tumor hypoxia in patients with pretreatment Hgb levels less than 13 g/dL compared with those who had Hgb levels of 13 g/dL or higher (12).

Treatment

From 1990 to 1996 patients were treated with 70 to 72.5 Gy accelerated hyperfractionated RT (1.25 Gy b.i.d.) and CCT consisting of 2 cycles of cisplatin (CDDP :12 mg/m^2/d $\times$ 5 days) and continuous infusion 5-fluorouracil (5-FU: 600 mg/m^2/d $\times$ 5 days) during Week 1 and Week 6. Two additional cycles of CDDP and 5-FU were planned after the completion of all local therapy.

The treatment program was modified after completion of the randomized trial. For the purpose of logistical simplicity, concurrent chemotherapy was delivered during Week 1 and Week 5 rather than during Week 1 and Week 6. The 2 additional cycles of postradiation chemotherapy were discontinued because of poor compliance during the randomized trial. The RT fields and doses were not altered. Some patients participated in 2 placebo-controlled trials of recombinant human keratinocyte growth factor (rHuKGF) during this latter period. They received the same treatment program, except that the dose of 5FU was 800 mg/m^2/d and the CDDP dose was 20 mg/m^2/day.

Statistical analysis

Descriptive statistics and frequency distributions were generated for the demographic and disease-related characteristics of the study population. The primary endpoint was failure-free survival (FFS). Any isolated or combined local, regional, or distant recurrence was counted as a failure event. FFS was defined as the time from the start of RT to the date of the first occurrence of failure. Local-regional control (LRC) and overall survival (OS) were evaluated as secondary endpoints and were defined similarly. For each outcome measure, curves by baseline Hgb category ($<$13 g/dL and $\leq$13 g/dL) were estimated using the Kaplan Meier product-limit method. The curves were compared by use of the log-rank test. Multivariable Cox proportional hazards models were used to examine potential risk factors for each outcome. These risk factors included age, gender, T-stage, primary site (oropharynx vs. other) and N-stage, in addition to the baseline Hgb category. Statistical significance was defined as $p \leq 0.05$ with no multiplicity adjustment.

RESULTS

Patient characteristics

One hundred fifty-nine patients were treated from 1990 to 2000. Sixteen participated in the trials of rHuKGF. The mean patient age was 57.3 years (range, 29.5–77.1 years). The median follow-up duration of surviving patients was 42 months (range, 4–129 months). The patient and treatment characteristics, stratified by Hgb level, are shown in Table 1. The overall mean ($\pm$ SD) pretreatment Hgb level was 13.3 g/dL (1.7 g/dL). No statistically significant difference existed between the low and normal Hgb patients with regard to tumor size, N-stage, RT dose, overall treatment time, age, or gender, but significant differences existed with regard to primary site ($p = 0.02$) and T-stage ($p < 0.01$). The normal Hgb group contained a higher proportion of patients with oropharyngeal primaries (52% vs. 26%) and a lower percentage of patients with T3 to T4 disease (78% vs. 92%). Because this study was a retrospective study, Karnofsky performance status (KPS) was not prospectively recorded on many of the patients and, therefore, was not included in the univariate or multivariate analyses.

Change in hemoglobin levels

The median (interquartile range, 25–75%) decrease in Hgb during RT/CCT was 2.2 (1.3–3.1) g/dL. The magnitude of the drop in Hgb during therapy was not statistically different in patients who recurred compared with those who remained disease-free. A steady decline in Hgb was observed during the treatment with the nadir around 5 to 7 weeks for most patients. Five weeks after completion of treatment, Hgb levels started to rebound. These findings are shown in Fig. 1.

Patterns of failure

A total of 49 failures occurred: 27 (55%) local failures, 3 (6%) regional node failures, and 16 (33%) distant failures. One (2%) patient had simultaneous local and regional failure and 2 (4%) patients had simultaneous regional and distant failure.

FFS, LRC, and OS

The 5-year probability of FFS for the entire group of 159 patients was 63%. Ninety-four percent (46/49) of failures occurred within 2 years of diagnosis. For patients with pretreatment Hgb levels of 13 g/dL or higher and less than 13 g/dL, 5-year FFS was 75% (95% CI, 65–85%) and 50% (95% CI, 31–69%), respectively ($p = 0.0192$) (Fig. 2). On univariate analysis, Hgb level, T-stage, and N-stage were significant predictors of FFS. However, on multivariate analysis, only Hgb level and T-stage were significantly associated with FFS (Table 2).

The 5-year probability LRC for the entire group of 159 patients was 79%. Ninety-four percent (31 of 33) of local-regional failures occurred within 2 years of diagnosis. For patients with pretreatment Hgb levels of 13 g/dL or higher, the 5-year LRC was 88% (95% CI, 81–95%) vs. 64% (95% CI, 42–86%) for patients with Hgb less than 13 g/dL ($p = 0.0353$) (Fig. 3). Hgb level was the only significant predictor of LRC on both univariate and multivariate analysis (Table 3).