Radiotherapy-Associated Anemia: The Scope of the Problem

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ABSTRACT

The impact of anemia on cancer patients undergoing chemotherapy is well established, but only recently has the prevalence of anemia in patients receiving radiotherapy received much attention. Many cancer patients present with anemia prior to radiotherapy, and even more experience anemia or a worsening of anemia at some point during treatment. However, the problem of anemia is often ignored because patients may experience only functional anemia, defined as a hemoglobin level less than 12 g/dl. Unless physiologic anemia (hemoglobin = 8 g/dl) is discovered, efforts to correct anemia are often not made. Because hemoglobin levels <12 g/dl seem to be associated with tumor hypoxia and poorer outcomes of radiotherapy in a number of patient populations, ignoring even modest anemia can result in decreased locoregional control, overall survival, and quality of life (QOL). Because increasing hemoglobin levels 1-2 g/dl is usually easily accomplished, there exists the potential for improving outcomes by paying greater attention to this problem. This article focuses on the prevalence of anemia, particularly functional anemia, and discusses the impact of anemia on locoregional control, overall survival, and QOL. The Oncologist 2000;5(suppl 2): 1-7

INTRODUCTION

Continuing advances in oncology care, including new radiotherapy technologies and recent developments with multimodal therapies, have significantly improved clinical outcomes and quality of life (QOL) for many patients with cancer. However, the prevalence and impact of cancer-associated anemia is not widely appreciated. Emerging data demonstrate that cancer-related anemia is unexpectedly common in cancer patients receiving radiotherapy and/or chemotherapy and that even modest anemia (hemoglobin <12 g/dl) substantially impairs QOL. In addition, a growing body of literature suggests that hemoglobin concentrations of less than 12-13 g/dl during cancer therapy are associated with reduced local tumor control and decreased survival [1, 2]. Although anemia of this magnitude can be easily managed, it is often overlooked or considered clinically insignificant. However, restoration of normal hemoglobin concentrations in patients undergoing radiotherapy has the potential to improve local tumor control and survival and produce sizable improvements in patient QOL.

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numbers indicate that anemia is a common problem for a majority of patients undergoing radiotherapy. Given the impact of anemia on local control and QOL, this is a problem that needs to be addressed in a more comprehensive manner.

To assess the prevalence of anemia according to tumor type, we stratified the data according to anatomical site. The data show that for patients with breast, prostate, colorectal, lung and bronchus, and uterine-cervix cancers, the percentage experiencing anemia increased during the course of radiotherapy (Fig. 1). The most notable increase occurred in the prostate cancer group. Only 5% of patients with prostate cancer presented with anemia, but roughly one-third (32%) were anemic by the end of their treatment. More uterine-cervix cancer patients presented with anemia (67%) than any other group, and by the end of radiotherapy 82% had experienced anemia. This number will more than likely increase as more uterine-cervix cancer patients receive combination therapy.

When we examined the data for uterine-cervix cancer patients with anemia, we discovered that for most patients, the severity of anemia before and during therapy was modest (Fig. 2). Of the 67% of patients who were anemic upon presentation, 44% had hemoglobin levels between 10 g/dl and 11.9 g/dl. Of the 82% who were anemic at some point during treatment, over half (59%) had hemoglobin levels between 10 g/dl and 11.9 g/dl. For both groups, 11% had hemoglobin levels between 9 g/dl and 9.9 g/dl. Only a few in either group had levels below 8.9 g/dl. Data on colorectal and prostate (Fig. 3), lung, and breast cancer patients (Table 1) yielded similar information. The current practice of treating breast cancer patients with lumpectomy and adjuvant chemotherapy prior to radiotherapy results in a high incidence of anemia among patients immediately before undergoing radiotherapy. In our study, 28 breast cancer patients received chemotherapy prior to radiotherapy. Of these, nearly 68% presented with anemia prior to radiotherapy, most (57%) having only modest anemia (hemoglobin level between 11.0 and 11.9 g/dl). Most of the 202 patients we reviewed so far had modest, or functional, anemia, which is often not treated. Very few had physiologic anemia (hemoglobin of 8 g/dl or less), which is more apt to receive attention.

**Understanding the Impact of Anemia**

In 1951 Hollaender et al. published their study on the radiosensitivity of aerobically and anaerobically cultured Escherichia coli [5]. Their study helped form the foundation of current thinking on tumor hypoxia and its effect on radiotherapy. Under hypoxic conditions, tumors appear to be less susceptible to radiation, and clinical outcomes are poorer [6]. A recent study investigated the relationship between tumor hypoxia and tumor control and survival in patients with cervical cancer undergoing radiotherapy. The results of tumor oxygenation measurements taken prior to radiotherapy by an Eppendorf oxygen electrode and measured by the Eppendorf pO₂ histograph indicate that tumor hypoxia is associated with an increased risk of relapse and death, particularly in patients with bulky hypoxic tumors. Tumor oxygenation was significantly associated with disease-free survival (\(p = 0.02\)), as was tumor size (\(p = 0.0003\)), stage (\(p = 0.006\)), and pretreatment hemoglobin level (\(p = 0.001\)) [7].

The association between anemia and tumor hypoxia is not fully understood, but it is well established that low hemoglobin levels independently predict poorer survival and relapse [8-10]. However, it is not clear whether low

![Figure 1](http://theoncologist.alphamedpress.org/)
hemoglobin levels are associated with poor survival because they indicate advanced disease or because they indicate poor tumor oxygenation. Current thinking, however, recognizes anemia as a likely contributor to tumor hypoxia \[8, 11\] with a focus on anemia and locoregional failure.

The impact of anemia on survival and relapse after radiotherapy has been investigated for a number of tumor types \[8, 9\]. A recent study looked at the association between anemia and overall survival and local tumor control in patients with locally advanced head and neck cancer undergoing radiation therapy. Patients were stratified by hemoglobin levels and were given either radiation therapy with a hypoxic cell sensitizer, etanidazole, or radiation therapy alone. The survival rate at five years for patients with anemia — defined as hemoglobin concentration <14.5 g/dl for men and <13 g/dl for women — was 22%. For nonanemic patients the rate at five years was 36%, a significant increase compared with anemic patients \(p = 0.0016\). Treatment with etanidazole did not significantly improve survival among any group of patients. Locoregional failure at five years differed significantly between patients with or without anemia. Patients with normal hemoglobin levels experienced locoregional failure at a rate of 52% compared with 68% for anemic patients \(p = 0.00028\) \[3\]. Again, the addition of etanidazole did not significantly affect locore-

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### Table 1. Distribution of anemia before and during radiation therapy (RT) in patients with breast cancer \(n = 63\) in the Beth Israel Medical Center/St. Luke’s-Roosevelt Hospital Center retrospective chart review

| Hemoglobin concentrations | Baseline \(n (%)\) | During RT \(n (%)\) | Patients who received pre-RT chemotherapy \(n = 28\)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with anemia</td>
<td>26 (41.2)</td>
<td>28 (44.4)</td>
<td>19 (67.9)</td>
</tr>
<tr>
<td>Hemoglobin concentrations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.0–6.9 g/dl</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7.0–7.9 g/dl</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8.0–8.9 g/dl</td>
<td>2 (3.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9.0–9.9 g/dl</td>
<td>3 (4.8)</td>
<td>4 (6.3)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>10.0–10.9 g/dl</td>
<td>5 (7.9)</td>
<td>5 (7.9)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>11.0–11.9 g/dl</td>
<td>16 (25.4)</td>
<td>19 (30.2)</td>
<td>16 (57.1)</td>
</tr>
</tbody>
</table>

### Figure 2. Results of Beth Israel Medical Center/St. Luke’s-Roosevelt Hospital Center retrospective chart review assessing the incidence of anemia, defined as hemoglobin concentration <12 g/dl, before and during radiation therapy in cervix cancer patients. The data, grouped by hemoglobin levels, are for 27 patients with cervix cancer.

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Figure 2. Results of Beth Israel Medical Center/St. Luke’s-Roosevelt Hospital Center retrospective chart review assessing the incidence of anemia, defined as hemoglobin concentration <12 g/dl, before and during radiation therapy in cervix cancer patients. The data, grouped by hemoglobin levels, are for 27 patients with cervix cancer.
Regional control among any group of patients. Anemia was significantly related to decreased survival and increased relapse rates.

A strong correlation between hemoglobin levels, local control, and survival was also observed in a study of 109 patients with T1-T2 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy [9]. Patients who presented with hemoglobin values >13.0 g/dl had significantly higher two-year rates of locoregional tumor control (95% versus 66%, \( p = 0.0018 \)) and survival (88% versus 46%, \( p < 0.001 \)) as compared with patients with hemoglobin values <13.0 g/dl.

Improving the efficacy of radiation therapy and, therefore, locoregional response and survival, may be achieved by addressing anemia and tumor hypoxia. Recent studies have investigated strategies that reduce anemia and tumor hypoxia such as hypoxic cell sensitizers, fluosol, carbogen breathing, hyperbaric oxygen, red blood cell transfusions, and recombinant human erythropoietin (epoetin alfa). In a study of patients with head and neck cancer given radiation and mitomycin C, a hypoxic cell sensitizer, or radiation alone, the data showed that the addition of mitomycin C significantly improved local recurrence-free survival and cause-specific survival (Figs. 4 and 5) [12]. In a preliminary study, advanced head and neck cancer patients treated with daily chemoradiotherapy received carbogen breathing, blood transfusions, or erythropoietin to increase their hemoglobin levels to nonanemic levels (≥13 g/dl) in order to overcome tumor hypoxia. A 100% complete response rate was observed. At 18 months, 6% had local recurrence and 14% had distant metastasis. Carbogen breathing and anemia correction resulted in improvements in local control, cause-specific survival, and overall survival (Fig. 6) [13].

Figure 3. Results of Beth Israel Medical Center/St. Luke’s-Roosevelt Hospital Center retrospective chart review assessing the incidence of anemia, defined as hemoglobin concentration <12 g/dl, before and during radiation therapy in patients with prostate cancer. The data, grouped by hemoglobin levels, are for 19 patients with prostate cancer.

Figure 4. Results from the trial reported by Haffty et al. [12]. Local recurrence-free survival in patients with head and neck cancer receiving radiation plus a radiosensitizer or radiation alone as adjuvant radiotherapy after surgery. Reprinted with permission.
Aggressive management of anemia, when incorporated into the overall management strategy for advanced head and neck cancer, has the potential to provide significant improvements in clinical outcomes. In addition to the head and neck data just discussed [9, 13], opportunities exist in other sites. In patients with cervical cancer undergoing radiotherapy with or without chemotherapy, those who maintained an average weekly nadir hemoglobin level (ANWH) above 12 g/dl experienced a decrease in pelvic and distant recurrence ($p < 0.0001$ and $p < 0.0005$, respectively) compared with those whose ANWH fell below 12 g/dl. In this study, patients whose hemoglobin fell below 10 g/dl, 11 g/dl, or 12 g/dl, depending upon the study site, received blood transfusions in order to maintain ANWH above these levels [2]. Finally, in patients with advanced cervical cancer, those patients who maintained hemoglobin levels above 10 g/dl during radiotherapy had improved locoregional tumor control compared with those patients whose on-therapy values fell below 10 g/dl ($p < 0.01$) [11].

Professional awareness of the human and economic costs of anemia in patients with cancer has progressed substantially in the last decade. Most recently, research completed by The Fatigue Coalition has revealed the profound burden that fatigue imposes on patients with cancer and...
their caregivers [4, 14]. In turn, recent studies have shown that modest improvements in hemoglobin concentrations can result in significant improvements in patient QOL. A recent study of epoetin alfa use in patients receiving chemotherapy demonstrated that increases in hemoglobin of less than 2 g/dl resulted in significantly improved QOL according to a questionnaire (Functional Assessment of Cancer Therapy-Anemia; FACT-An) and linear analog scale assessment (LASA) [15]. QOL improvements were observed independent of response to chemotherapy. Another study of erythropoietin use in patients undergoing chemotherapy demonstrated significant improvements in LASA scores, indicating improvement in QOL. The mean increase in hemoglobin in this study was only 1.8 g/dl [16].

Even modest anemia has a detrimental effect on clinical outcomes. Dubray [17] reported a study of head and neck cancer patients receiving radiotherapy and demonstrated that high pretreatment hemoglobin significantly related to higher survival rates. In this study, those with anemia had functional, not physiologic, anemia. All but 3 of 63 patients with anemia—defined as hemoglobin <13.5 g/dl for men and hemoglobin <12.0 g/dl for women—had hemoglobin >10 g/dl [17]. Because most of our patients also had anemia that was modest and “functional,” we believe the same opportunities exist to improve outcomes.

CONCLUSIONS

Greater awareness of the prevalence and impact of anemia in patients with cancer is an important goal for all clinicians. Although raising hemoglobin levels by 1 or 2 g/dl to 12 g/dl is easily done, historically, radiation oncologists have not given ample attention to treating moderate, or functional, anemia. The data we are collecting at Beth Israel Medical Center and St. Luke’s-Roosevelt Hospital Center highlight the prevalence of anemia in cancer patients. We are seeing similar data for a number of tumor sites. Increasing attention is being given to the detrimental impact anemia has on QOL, local tumor control, and overall survival. Therefore, managing anemia, even mild-to-moderate anemia, with an approach that minimizes risk to the patient and reduces undesirable side effects, is imperative if patients are to preserve QOL and improve outcomes of radiotherapy.

REFERENCES

