Anemia Treatment and the Radiation Oncologist: Optimizing Patient Outcomes

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Anemia is a frequent complication of cancer and its associated treatment. Although its occurrence is well documented in the chemotherapy setting, the prevalence and nature of anemia in the radiation oncology setting major advances in the technology and techniques of radiation oncology have improved our ability to attain local tumor control with decreased tissue complications. The broad objectives of ongoing research in the radiation oncology setting include (1) further increasing locoregional tumor control rates, which may translate into better survival; (2) evaluating radiochemotherapy regimens that contain a new generation of cytotoxic agents, some with radiosensitizing properties, in an effort to improve local control and to decrease the incidence of distant metastases; and (3) maintaining or improving patient quality of life during and after therapy.

‘Anemia of Chronic Disease’

Maintaining or improving a cancer patient’s functional and psychosocial status is particularly important in this era of aggressive combined-modality and high-dose treatment strategies. Anemia, the most frequent hematologic abnormality in the cancer population (including patients presenting for or undergoing radiation therapy) is associated with symptoms (eg, fatigue, dizziness, shortness of breath) that may greatly impair quality of life. At the time of cancer diagnosis, this condition is typically categorized as "anemia of chronic disease"; it may be aggravated over time by underlying disease progression, surgical blood loss, or subsequent chemotherapy and/or radiation therapy. Until recently, oncologists did not routinely treat mild-to-moderate anemia because it was perceived as "clinically unimportant" when placed in the context of life-threatening complications, including other hematologic abnormalities. However, this perception is changing among medical oncologists. Recent studies indicate that correcting mild-to-moderate anemia in cancer patients can improve energy levels,[1,2] which may have a profound effect on functional capacity, sense of well-being, and ultimately, the desire to continue chemotherapy.

Two surveys of cancer patients found that fatigue is highly prevalent during chemotherapy or chemoradiation and is associated with substantial adverse effects on physical and psychosocial functioning.[3,4] In the more recent survey, most patients reported that fatigue was prolonged and had a greater impact on their daily lives than pain, nausea, and depression.[4] Although many factors can induce or exacerbate cancer-related fatigue,[5] anemia is one of the more common etiologies. Several studies show that cancer patients with higher hemoglobin levels experience less fatigue and have more favorable perceptions of their quality of life.[6-8] Fatigue also is a well-recognized adverse effect of fractionated radiation therapy, but its causes are poorly understood. The prevalence of fatigue increases steadily over the course of radiation therapy, often peaking after several weeks.[9-12]

In the radiation oncology setting, transfusions are generally performed to correct "severe" anemia (ie, hemoglobin levels < 8 g/dL or pronounced symptoms),[13,14] and unless contraindicated, transfusions should be performed in such cases. Nevertheless, correcting mild-to-moderate anemia may have positive effects on quality of life.[1,2,7] Moreover, emerging data suggest that pretreatment anemia and low hemoglobin levels during radiation therapy are risk factors for poor locoregional control and survival.

Prevalence of Anemia in Radiation Oncology

Radiation oncologists often "inherit" anemia that has developed from surgical blood loss, myelotoxic chemotherapy, and/or advanced disease. The prevalence of anemia among patients presenting for radiation therapy is not well documented, but it is generally believed that a substantial proportion of
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these patients do become anemic. A recent literature review revealed a relatively high incidence of mild-to-moderate anemia in patients receiving single-agent or combination chemotherapy for nonmyeloid malignancies.[15] A similar assessment in the radiation oncology setting is not available. An ongoing retrospective study at the Beth Israel Medical Center is assessing the prevalence of anemia (defined as hemoglobin < 12 g/dL) immediately prior to and during radiation therapy.[16] We are performing this study through random chart sampling of patients who had received radiation therapy since December 1996. As of June 1999, a total of 574 patients were evaluable, with a relatively even distribution of cancers of the prostate (16%), breast (14%), head/neck (12%), colon/rectum (11%), lung/bronchus (11%), and uterine cervix (9%). The overall prevalence of anemia (hemoglobin < 12 g/dL) at presentation for radiation therapy was approximately 41% (28% and 54% of men and women, respectively). At completion of radiation therapy, 43% of men and 63% of women had anemia (overall prevalence of 54%), which usually was of mild-to-moderate severity (ie, hemoglobin levels of 10 to 12 g/dL).

The subset of patients with cancer of the uterine cervix had the highest prevalence of anemia at baseline (75%) and at completion of radiation therapy (79%), whereas prostate cancer patients had the lowest prevalence of anemia at both evaluation points (9% and 26%, respectively). The prevalence of anemia increased substantially during radiation therapy in patients with prostate cancer and those with colorectal (44% to 63%), lung/bronchus (55% to 77%), or head/neck (34% to 57%) cancer. Across all tumor subsets, low hemoglobin levels typically ranged from 10 to 12 g/dL. The preliminary findings of this study show that mild-to-moderate anemia is a common problem in radiation oncology, both at presentation and at completion of radiation therapy. It appears that most radiation oncology patients with anemia (60% to 80%) have hemoglobin levels that could be corrected easily (10 to 12 g/dL). A final patient database of more than 1,000 patients is anticipated. To our knowledge, this is the first large-scale study designed to systematically characterize the prevalence and nature of anemia in the radiation oncology setting.

**Significance of Anemia in Radiation Oncology**

The ability of anemia to impair quality of life in cancer patients has become more appreciated in recent years. There also appears to be a relationship between anemia and low rates of disease control and survival in the radiation oncology setting. An extensive body of literature provides evidence of an association between low hemoglobin levels and low locoregional control/survival following curative-intent radiation therapy. This association has been studied most widely in patients receiving fractionated radiotherapy for cervical[17-21] or head and neck cancer.[22-26]

**Proposed Mechanisms**

Regression analyses have consistently shown that baseline anemia (variably defined) is an independent predictor of locoregional control and disease-free or overall survival in these patients.[17-26] The presumed link between low hemoglobin levels and poor locoregional control of solid tumors is molecular oxygen, a well-known radiosensitizer (Figure 1). Numerous studies have identified intratumoral hypoxia as an adverse prognostic factor for locoregional control and survival in patients receiving definitive radiation therapy for cervical cancer or head and neck cancer.[27,28] In addition, preradiation hypoxia has been associated with an increased risk of distant metastases in patients receiving radiation therapy plus hyperthermia for soft-tissue sarcomas.[29]

Low hemoglobin levels have been correlated with poor intratumoral oxygenation.[30,31] For example, in a recent study by Strauss et al, a baseline hemoglobin level < 13 g/dL was associated with a low intratumoral pO_2_ level in patients undergoing radiation therapy for advanced cervical cancer.[31] Although it is speculated that low hemoglobin levels exacerbate the preexisting hypoxic condition of solid tumors, this relationship and its relevance in the clinical setting remain controversial.[26,31-33]

**Hemoglobin Values**

Interestingly, hemoglobin levels of 12 to 14 g/dL have been used to stratify patients in selected cervical[34] and head and neck cancer studies.[22-26] suggesting that hemoglobin values within this range (rather than a threshold of 10 g/dL) should prompt consideration of anemia-directed interventions. One of the most recently published investigations of the effect of anemia on radiation therapy outcomes involved approximately 600 patients with cervical cancer.[34] In this Canadian study, an average weekly nadir hemoglobin level of 12 g/dL or more during radiation therapy was associated with significantly improved rates of local/distant disease recurrence and 5-year survival.[34]

Investigators at the Fox Chase Cancer Center found that T1/2 glottic carcinoma patients with
preradiation therapy hemoglobin levels > 13 g/dL achieved higher 2-year local control and survival rates (95% and 88%, respectively) than did patients with hemoglobin levels below this threshold (66% and 46%, respectively).[23] In fact, hemoglobin level was the only factor that significantly influenced both local control and survival on regression analysis.[23]

In a recent study by the Radiation Therapy Oncology Group (RTOG), stage III/IV head/neck squamous cell carcinoma patients who had low hemoglobin levels (ie, < 14.5 g/dL for men and < 13 g/dL for women) early in the course of radiation therapy showed less favorable 5-year locoregional failure and survival rates (68% and 22%, respectively), as compared with patients who had higher hemoglobin levels (52% and 36%, respectively).[24]

Other Subgroups
Growing evidence suggests that pretreatment anemia influences radiation therapy outcomes in other tumor types, including non-small-cell lung,[35-38] prostate,[39] and anal cancers.[40] Although less extensively documented, a decrease in hemoglobin levels during radiation therapy also appears to adversely affect locoregional disease control and survival.[19,41-46]

Potential Strategies for Overcoming Hypoxia
Correction of anemia and the use of hypoxia-directed therapies, such as hypoxic-cell sensitizers, have the potential to influence disease outcomes in the radiation oncology setting. Early correction of mild-to-moderate anemia may be viewed as a means of delaying the development and progression of intratumoral hypoxia. The combination of anemia- and hypoxia-directed interventions is a reasonable consideration prior to initiating a course of radiation therapy.

Hypoxic-Cell Sensitizers
Targeting of the hypoxic environment of solid tumors is one approach to overcoming hypoxia in clinical practice. Hypoxic-cell sensitizers have a direct effect on DNA, conferring cytotoxicity independent of the administration of radiation therapy.[47] Clinical trials have evaluated mitomycin (Mutamycin), as an adjunct to radiation therapy in patients with cancers of the head and neck, cervix, and other sites.[47-53] Analyses of pooled data from two similarly designed randomized trials demonstrated that the addition of mitomycin to radiation therapy in head and neck cancer patients results in statistically and clinically significant improvements in local recurrence-free survival (85% vs 66% for radiation alone), locoregional recurrence-free survival (76% vs 54% for radiation alone), and cause-specific survival at 5 years (74% vs 51% for radiation alone).[47]

More recently, local control and survival rates in patients with head and neck cancer were found to be most favorable in those who received Vienna continuous hyperfractionated accelerated radiotherapy (V-CHART) plus mitomycin (48% and 39%, respectively) compared with those who received V-CHART alone (34% and 28%, respectively) or conventional fractionation (31% and 27%, respectively).[51,52]

Erythropoietin
Transfusion red blood cells is a somewhat unpopular anemia-directed intervention among patients and health-care providers, largely because of the well-known risks (eg, infections, acute/chronic reactions, immunosuppression) and inconvenience as well as continuing deficits in the blood supply.[33,54] Alternatively, recombinant human erythropoietin (epoetin alfa, Epogen, Procrit), may be used for the treatment of chemotherapy-related anemia in patients with nonmyeloid malignancies.

In phase I/II studies, erythropoietin was well tolerated and increased hemoglobin levels in patients who were anemic prior to radiation therapy—the mean hemoglobin increase during radiation therapy was approximately 0.60 g/dL per week.[13,55-58] Most of these studies used erythropoietin at 150 U/kg administered three times weekly (starting at least 1 week prior to radiation therapy) with supplemental iron. Our experience in the radiation oncology setting has been that normal hemoglobin can usually be attained within 2 to 3 weeks of initiating this therapy in patients with mild-to-moderate preradiation anemia. Once-weekly erythropoietin may be equally effective in increasing hemoglobin levels and reducing transfusion requirements during chemotherapy and chemoradiation, as recently demonstrated in community-based studies.[59,60]

The preliminary results of the more recent study, which focused on patients who were receiving sequential or concurrent chemoradiation, showed that the mean increase in hemoglobin levels over the 16-week treatment period was 2.0 g/dL (ranging from 1.8 to 3.4 g/dL, depending on the chemotherapy component).[60] Complete normalization of hemoglobin levels prior to initiation of radiation therapy may not be critical as long as patients are being actively treated for anemia. The hematopoietic effects of erythropoietin during radiation therapy have prompted investigation of its
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Effects on Locoregional Control and Survival—The prognostic significance of preradiation anemia in patients with head and neck and cervical cancer would suggest that raising hemoglobin levels to the normal range may translate into improved survival. There is also suggestive evidence that correcting anemia with erythropoietin improves locoregional tumor control and survival following radiation or chemoradiation for head and neck cancer.[61-63]

In a study by Glaser et al, 37 patients with a baseline hemoglobin level < 12.5 g/dL received erythropoietin three times weekly during a fluorouracil-based neoadjuvant chemoradiation regimen for oral squamous cell carcinoma.[64] The proportion of patients with residual disease at the time of surgical resection was significantly lower among these patients compared with the historical control group, which did not receive erythropoietin (32% vs 73%, *P* = .001).[64] Moreover, local recurrences were noted in 11% of patients treated with erythropoietin and 30% of the control group after a 17-month follow-up period (*P* = .03).[64]

A subsequent study by Glaser et al suggested that 2-year locoregional control and survival rates improved with the use of erythropoietin three times weekly in patients with anemia (hemoglobin level < 14.5 g/dL) at the initiation of chemoradiation for oral cavity and oropharyngeal cancer.[65] The 2-year locoregional control rates were 95% in anemic patients who received erythropoietin, 88% in those without pretreatment anemia, and 72% in anemic patients who did not receive erythropoietin during chemoradiation.[65] The overall survival rates reported for these groups of patients were 93%, 84%, and 62%, respectively.[65]

A prospective Southwest Oncology Group (SWOG) study evaluated the effect of erythropoietin plus oral iron on the progression-free and overall survival of 52 patients receiving concurrent cisplatin (Platinol) and pelvic irradiation for stage IIB to IVA cervical cancer.[66] The mean hemoglobin levels were 10.3 g/dL at baseline and 12.0 g/dL at the completion of a 5-week course of chemoradiation, with a gradual increase during the study period. The target hemoglobin level of 12.5 g/dL was achieved by 40% of patients prior to receiving their 13th fraction of radiation. Among patients with confirmed disease responses, the overall response rate to chemoradiation was 60%, with a median progression-free interval of 15 months and a median survival duration of 23 months. This SWOG study was terminated early due to modest increases in hemoglobin levels noted during chemoradiation.

The RTOG is conducting a randomized phase III study of erythropoietin as an adjunct to radiotherapy in patients with head and neck cancer.[67] Comparative locoregional control and survival data are forthcoming and will provide further insight into whether correcting anemia during radiotherapy has an effect on long-term outcomes.

Effects on Quality of Life—Two small-scale radiation studies of erythropoietin therapy evaluated patient quality of life at weekly intervals and showed a trend toward improved quality-of-life benefits.[55,58] Large community-based studies of erythropoietin administered three times weekly or once weekly to over 7,500 anemic cancer patients undergoing chemotherapy or chemoradiation demonstrated comparably significant beneficial effects on self-reported energy levels, the ability to perform daily activities, and overall quality of life.[1,2,59,60] The preliminary results of another study of once-weekly erythropoietin as an adjunct to sequential or concurrent chemoradiation regimens further support these quality-of-life benefits.[60]

Conclusions

Based on data from Beth Israel Medical Center on the prevalence of anemia, hemoglobin levels within the range of 10 to 12 g/dL are common in the radiation oncology setting. Ongoing research efforts seek to characterize the relationship between the extent and rate of hemoglobin decline and the development of fatigue, as well as the influence of anemia on other quality of life measures, in the cancer population. Strategies such as hypoxic-cell sensitizers (mitomycin) and anemia-directed therapies (erythropoietin, blood transfusion) are reasonable interventions in patients planning to undergo radiation therapy. Managing mild-to-moderate anemia may potentially influence both tumor response and patient quality of life.

The long-term benefits of correcting anemia during radiation or chemoradiation therapy have yet to be established. The relationship between postradiation local control and survival, however, is not always clear, and any increase in survival may actually be disease-specific. As radiation oncologists, we must place greater emphasis on diagnosing and managing anemia, with the goal of improving disease outcomes and patient well-being.
References:


67. Machtay M: Phase III randomized study of radiotherapy with or without epoetin alfa in anemic

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