Hypoxia and Anemia: Factors in Decreased Sensitivity to Radiation Therapy and Chemotherapy?

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ABSTRACT

Hypoxia is a common feature of solid tumors that occurs across a wide variety of malignancies. Hypoxia and anemia (which contributes to tumor hypoxia) can lead to ionizing radiation and chemotherapy resistance by depriving tumor cells of the oxygen essential for the cytotoxic activities of these agents. Hypoxia may also reduce tumor sensitivity to radiation therapy and chemotherapy through one or more indirect mechanisms that include proteomic and genomic changes. These effects, in turn, can lead to increased invasiveness and metastatic potential, loss of apoptosis, and chaotic angiogenesis, thereby further increasing treatment resistance. Investigations of the prognostic significance of pretreatment tumor oxygenation status have shown that hypoxia (oxygen tension [pO2] value ≤10 mmHg) is associated with lower overall and disease-free survival, greater recurrence, and less locoregional control in head and neck carcinoma, cervical carcinoma, and soft-tissue sarcoma. In view of the deleterious effect of hypoxia on standard cancer treatment, a variety of hypoxia- and anemia-targeted therapies have been studied in an effort to improve therapeutic effectiveness and patient outcomes. Early evidence from experimental and clinical studies suggests the administration of recombinant human erythropoietin (rHuEPO) may enhance the effectiveness of radiation therapy and chemotherapy by increasing hemoglobin levels and ameliorating anemia in patients with disease- or treatment-related anemia. However, further research is needed in the area of hypoxia-related treatment resistance and its reversal.

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Explain how tumor hypoxia affects radiation resistance.
2. Apply this understanding to clinical outcome in specific diseases.
3. Describe approaches for improving therapeutic outcome in anemia patients.

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ABSTRACT

Hypoxia is a common feature of solid tumors that occurs across a wide variety of malignancies. Hypoxia and anemia (which contributes to tumor hypoxia) can lead to ionizing radiation and chemotherapy resistance by depriving tumor cells of the oxygen essential for the cytotoxic activities of these agents. Hypoxia may also reduce tumor sensitivity to radiation therapy and chemotherapy through one or more indirect mechanisms that include proteomic and genomic changes. These effects, in turn, can lead to increased invasiveness and metastatic potential, loss of apoptosis, and chaotic angiogenesis, thereby further increasing treatment resistance. Investigations of the prognostic significance of pretreatment tumor oxygenation status have shown that hypoxia (oxygen tension [pO2] value ≤10 mmHg) is associated with lower overall and disease-free survival, greater recurrence, and less locoregional control in head and neck carcinoma, cervical carcinoma, and soft-tissue sarcoma. In view of the deleterious effect of hypoxia on standard cancer treatment, a variety of hypoxia- and anemia-targeted therapies have been studied in an effort to improve therapeutic effectiveness and patient outcomes. Early evidence from experimental and clinical studies suggests the administration of recombinant human erythropoietin (rHuEPO) may enhance the effectiveness of radiation therapy and chemotherapy by increasing hemoglobin levels and ameliorating anemia in patients with disease- or treatment-related anemia. However, further research is needed in the area of hypoxia-related treatment resistance and its reversal. The Oncologist 2004;9(suppl 5):31-40

INTRODUCTION

Hypoxia is a characteristic pathophysiologic property of solid tumors that occurs across a wide range of experimental and human malignancies [1]. Hypoxic regions, defined as areas with oxygen tension (pO2) values of 10 mmHg or lower, have been identified in locally advanced breast [1] and
cervical [2] tumors and have been found to have a prevalence of approximately 60% in both tumor types investigated. Hypoxic regions have also been identified in head and neck cancer [3-6], rectal cancer [7, 8], prostate cancer [9, 10], pancreatic cancer [11], brain tumors [12, 13], soft-tissue sarcomas [14, 15], and malignant melanoma [16].

A growing body of evidence suggests that tumor hypoxia, acting through direct or indirect mechanisms, or both (Fig. 1), may contribute to resistance to standard radiation therapy, some chemotherapy, and chemoradiation, and subsequently, to poorer clinical outcome [1, 17]. Hypoxia may directly induce tumor resistance to radiation therapy and certain chemotherapeutic agents via deprivation of molecular oxygen, because such therapies require adequate intratumoral oxygen to be maximally cytotoxic. Indirectly, hypoxia may lead to treatment resistance by modulating (stimulating or inhibiting) gene expression and posttranscriptional or posttranslational effects, resulting in changes of the proteome that subsequently lead to alterations of proliferation kinetics, cell-cycle position, or numbers of cells remaining in the G0 phase, thereby influencing the number of cells destroyed by radiation therapy or chemotherapy [1, 17, 18]. Hypoxia-induced proteomic changes may also lead to changes in cellular metabolism (e.g., induction of the glycolytic pathway); increased enzyme activities; elevated intracellular concentrations of glutathione and associated thiols that can compete with the target DNA; and increased transcription of glucose transporters (e.g., glucose transporter 1 [GLUT-1], GLUT-3), DNA repair enzymes, growth factors (e.g., transforming growth factor beta [TGF-β]); and proteins involved in cell detachment, invasiveness, and resistance. Many hypoxia-inducible genes are controlled by the transcription factor hypoxia-inducible factor 1 (HIF-1), including those involved in erythropoiesis, angiogenesis, glycolytic metabolism, and tumor invasiveness.

In addition to proteomic changes, hypoxia may promote genomic instability and change, thereby increasing genetic diversity; further, hypoxia may exert strong selective pressure. Hypoxia has been found to create selection pressure against wild-type p53 in tumors by promoting apoptosis of such cells. This allows for the emergence of a dominant resistant cell population with mutant p53, since such cells would be resistant to apoptosis [2, 19-22].

**Tumor Hypoxia and Mechanisms of Resistance to Radiation Therapy**

Radiation therapy is an integral component of standard care for most locally advanced solid tumors, with chemotherapeutic agents generally administered concurrently for enhanced local tumor control [23, 24]. However, local recurrence may occur after radiation therapy, which portends a poor likelihood of long-term survival. While the primary factors leading to radioresistance and subsequent disease recurrence remain unclear [25], one factor currently believed to play an important role in determining the outcome of curative-intent radiation therapy is intratumoral hypoxia. As shown in Figure 2, radiosensitivity rapidly declines when...
tumor pO$_2$ is <25-30 mmHg [2]. Several explanations for this have been proposed. One involves the intratumoral control of molecular oxygen, a potent radiosensitizer concerned with mediation of DNA damage [25]. The presence of oxygen may increase DNA damage via formation of oxygen-derived free hydroxyl radicals, which occurs primarily after the interaction of radiation with intracellular water [26]. Alternatively, the presence of oxygen can stabilize (“fix”) the highly reactive hydroxyl radicals that cause DNA damage, thus reducing the ability of the tumor cells to repair the damaged DNA strands [27, 28]. Because of this oxygen-enhancement effect, the dose of single-fraction ionizing radiation required to achieve the same cell survival fraction is about two to three times higher under hypoxic conditions than under normoxic conditions; in other words, radiation therapy is about two to three times less effective in destroying hypoxic cells than normoxic cells [28]. Further, experimental studies have shown that surviving cells can re-establish tumors at the site of the original malignancy or in other areas following their transplantation [18]. The situation with fractionated radiotherapy is more complex, given the reoxygenation of the cells that occurs between treatments. With reoxygenation, the hypoxic tumor cells reacquire the radiosensitivity displayed by well-oxygenated cells, thereby increasing the responsiveness of the tumor to subsequent radiation therapy. However, the patterns of reoxygenation of the tumor cells are variable, and it is possible that some tumor cells reoxygenate less rapidly and extensively. These cells are, therefore, still relatively protected from radiation, continue to proliferate, and thereby limit the curability of the cancer by radiation therapy [18].

As indicated in Figure 1 and Table 1, hypoxia may also substantially enhance radioresistance by inducing proteomic and genomic changes that lead to increases in the number of tumor cells with diminished apoptotic potential or increased proliferative and metastatic potential, or that lead to increases in the levels of repair enzymes or heat shock proteins [29]. Heat shock proteins, for example, HSP70 and HSP27, function mainly as molecular chaperones, allowing cells to adapt to changes in the environment and survive otherwise lethal conditions [30]. HSP70 is highly expressed in malignant tumor cells of various origins, including human breast tumors, whereas in normal cells, its expression is induced mainly by stress [31]. In a study reported in 2000, Nylandsted et al. demonstrated that inhibition of HSP70 synthesis resulted in massive death of human breast cancer cells [31]. Among other actions, HSP70 inhibits apoptosis induced by a wide range of stimuli, notably via inhibition of a signaling pathway independent of the classical caspase cascade [32]. Expression of HSP70 has additionally been associated with increased cell proliferation, poor differentiation, lymph node metastases, and poor therapeutic outcome in human breast cancer [33-36].

The prognostic significance of low pretreatment pO$_2$ values for responsiveness of tumors to radiation therapy has been the subject of numerous clinical studies. Gatenby et al., who used polarographic electrodes to measure oxygenation in lymph-node metastases of head and neck cancer, appear

![Figure 2. Relative radiosensitivity of tumor cells as a function of tissue pO$_2$. Reprinted with permission from Vaupel et al. [2].](http://theoncologist.alphamedpress.org/)

### Table 1. Selected mechanisms for hypoxia-related tumor resistance to radiotherapy [6, 17, 59]

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Direct effects</strong></td>
<td>Through reduced “fixation” of DNA damage (x- and γ-rays)</td>
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<tr>
<td><strong>Indirect effects related to proteomic changes</strong></td>
<td></td>
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<tr>
<td>• Slowing of proliferation kinetics</td>
<td></td>
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<tr>
<td>• G$_s$/S-phase arrest; increase in number of cells in G$_0$ phase</td>
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<tr>
<td>• Elevated levels of glutathione and related thiols</td>
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<tr>
<td>• Elevated levels of DNA-repair enzymes and of resistance-related proteins</td>
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<tr>
<td><strong>Indirect effects related to genome changes</strong></td>
<td></td>
</tr>
<tr>
<td>• Loss of apoptosis and differentiation</td>
<td></td>
</tr>
<tr>
<td>• Clonal heterogeneity</td>
<td></td>
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<tr>
<td>• Proliferation of resistant clonal variants</td>
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<tr>
<td>• Increase in number of cells with aggressive phenotype</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary indirect effects related to intensified glycolysis and extracellular acidosis</strong></td>
<td></td>
</tr>
<tr>
<td>• Cell-cycle effects</td>
<td></td>
</tr>
<tr>
<td>• Activation of repair processes</td>
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</table>

*Resulting from modulation of gene expression, posttranscriptional effects, and/or posttranslational effects.*

*Through point mutations, gene amplification, and/or chromosomal rearrangements.*
to be the first group to have reported substantial differences in pO2 values in the tumors of patients who responded to radiation therapy, compared with tumors of nonresponders [29, 37]. With the introduction in 1989 of a computerized pO2 histography system, prospective clinical trials were initiated to investigate the relationship between tumor oxygenation and radiation response in various forms of cancer; results of several of these trials are summarized below.

**Hypoxia and Radiation Therapy Resistance in Head and Neck Cancer**

In a study in patients with advanced squamous cell carcinoma of the head and neck treated with radiation therapy, Nordsmark et al. found a lower rate of actuarial 2-year tumor control in patients with pretreatment median hypoxic fractions (defined as % pO2 values <2.5 mmHg) that were >15% versus those that were ≤15% (33% and 77%, respectively; p = 0.01) [3, 25]. Also, those patients who experienced locoregional failure had higher median hypoxic fractions than did patients who achieved locoregional tumor control (22% versus 6%) [3]. Brizel et al., in a study that compared radiation therapy outcomes in head and neck cancer patients with well-oxygenated versus poorly oxygenated primary tumors and metastatic lymph nodes, found that tumor hypoxia (median pO2 <10 mmHg) adversely affected 2-year locoregional control (30% versus 73%, p = 0.01), disease-free survival rate (26% versus 73%, p = 0.005), and overall survival rate (35% versus 83%, p = 0.02) [38]. Additionally, the investigators observed that nodes that were poorly oxygenated prior to treatment were more likely to contain viable residual disease at postradiation neck dissection. Rudat et al., in a more recent study, evaluated the repeatability and prognostic impact of pretreatment pO2 histography on survival in patients with advanced head and neck cancer treated with accelerated hyperfractionated radiation therapy with or without chemotherapy. Multivariate analysis showed the fraction of pO2 values ≤2.5 mmHg to be the only significant (p = 0.05) prognostic factor for survival after fractionated radiation therapy [39].

**Hypoxia and Radiation Therapy Resistance in Cervical Cancer**

Several studies have demonstrated that the pretreatment oxygenation status of tumors can predict overall survival, disease-free survival, and/or local tumor control in patients with cervical cancer [40-45]. In 1993, Höckel et al. reported preliminary data from a study of the clinical relevance of pO2 in patients undergoing radiation or surgery for advanced cancer of the uterine cervix [29, 40, 41]. Results of that 19-month (median) interim analysis indicated that a pO2 level ≤10 mmHg discriminated between hypoxic and nonhypoxic cervical cancers. Specifically, patients with median pO2 values >10 mmHg had significantly (p ≤0.002) higher rates of recurrence-free and overall survival than patients with lower pO2 values. Results obtained after a 28-month follow-up showed that patients in the surgical subgroup who had hypoxic tumors had significantly (p = 0.036) larger tumor extensions and significantly (p = 0.026) more frequent (occult) parametrial spread as well as more pronounced lymphovascular space involvement (p = 0.036) than patients who had nonhypoxic tumors [46, 47]. Further, patients with hypoxic tumors had significantly lower 5-year disease-free (p = 0.009) and overall survival (p = 0.004) probabilities than their nonhypoxic counterparts, irrespective of the type of primary therapy administered (Fig. 3A-3C and Fig. 4). Results of both univariate and multivariate analyses indicated that tumor oxygenation, expressed as median pO2, was the strongest independent predictor of overall (p = 0.006 and p = 0.004, respectively) and disease-free survival (p = 0.011 and p = 0.008, respectively) [46]. Knocke et al., in a study of patients with carcinoma of the uterine cervix treated with primary radiation therapy, found a 3-year disease-free survival rate of 69% for patients with pretreatment median pO2 values >10 mmHg versus 34% for patients with median pO2 values ≤10 mmHg (p < 0.02); corresponding values for local control were 47% and 84% (p = 0.05). Further, 70% of the patients who developed recurrent disease had median pO2 values <10 mmHg [25, 44]. Strauss et al., who also examined median pO2 in cervical cancer patients undergoing radiation therapy, found that a baseline pO2 <10 mmHg was an adverse prognostic factor for local control, but only in patients who experienced sustained hypoxia after a 2-week course of radiation. Local control at 1 year was 42% in that subgroup and lower than that observed in patients who had normoxic tumors at baseline (68%) or who experienced reoxygenation of hypoxic tumors at 2 weeks (83%) [48]. Sundfor et al. evaluated tumor hypoxia and vascular density as predictors of metastasis in squamous cell carcinomas of the uterine cervix [43]. Those investigators found that a high incidence of metastasis was associated with poor oxygenation of the primary tumor but not with high vascular density. In a subsequent study, Sundfor et al. demonstrated that the hypoxic subvolume of the tumor, that is, the tumor volume having pO2 values <5 mmHg, was a significant prognostic factor for locoregional control, disease-free survival, and overall survival [45].

**Hypoxia and Radiation Therapy Resistance in Other Cancers**

Results similar to those observed in patients with head and neck and cervical cancers have also been found in patients with soft-tissue sarcomas [14, 15]. Brizel et al., in a study in this population, found a significantly lower 18-month actuarial disease-free survival rate for patients with
median tumor pO2 values <10 mmHg than for patients with median tumor pO2 values >10 mmHg (35% versus 70%, \( p = 0.01 \)) [14]. Interestingly, the median pO2 for metastasiz- ing tumors was significantly lower than that for nonmetasta- sizing tumors (7.5 mmHg versus 20 mmHg, \( p = 0.03 \)).

Nordsmark et al., in a study that explored the relationship between tumor oxygenation and cell proliferation in soft-tis- sue sarcomas, found a significant \( (p = 0.04) \) correlation between the median pO2 and tumor cell potential doubling time, with the most rapidly proliferating tumor cells found in the most poorly oxygenated sarcomas. However, no correla- tion was detected between the level of hypoxia expressed by the percentage of pO2 values \( \leq 2.5 \) or \( \leq 5.0 \) mmHg and tumor cell potential doubling time [15].

Harrison et al. recently summarized the results of a series of studies (including several of those mentioned above) that demonstrate the adverse prognostic influence of a low pretreatment median pO2 value or a high pretreatment median hypoxic fraction on outcome in patients undergoing radiation therapy, radiation/surgery, or chemoradiation [25]. As indicated by those authors, further research is needed to clarify whether hypoxia is solely predictive of response to radiation therapy or whether it has prognostic value independent of therapy, possibly reflecting other hypoxia-related mechanisms, including promotion of tumor progression.

**Figure 3. Overall survival probabilities, stratified by tumor oxygenation, estimated by Kaplan-Meier methods for patients with advanced cancer of the uterine cervix treated with curative intent.**

A) Surgery or radiation therapy. B) Primary radiation therapy. C) Primary surgery. Reprinted with permission from Höckel and Vaupel [47].

**Figure 4. Disease-free survival probabilities estimated by Kaplan-Meier methods for patients treated with curative intent (i.e., surgery or radiation therapy), stratified by tumor oxygenation.** Reprinted with permission from Höckel et al. [46].

**TUMOR HYPOXIA AND RESISTANCE TO CHEMOTHERAPY**

As is the case with radiation therapy, the efficacy of some chemotherapeutic agents can be decreased by a variety of direct and indirect mechanisms (Table 2) [17, 18]. Poor and fluctuating blood flow (which leads to acute hypoxia) as well as increased diffusion distances (which lead to chronic hypoxia) can result in the diminished and erratic distribution of chemotherapeutic agents, with a consequent effect on their therapeutic efficacy [17, 49]. Also, some chemothera- peutic agents, for example, cyclophosphamide, carboplatin (Paraplatin®; Bristol-Myers Squibb; Princeton, NJ), and doxorubicin (Adriamycin®; Bedford Laboratories; Bedford, OH), have been shown to be oxygen dependent under both in vivo and in vitro conditions [18, 50-52]. Other mechani-sms that have been proposed as causes of chemoresistance...
are reduced generation of free radicals, thus limiting DNA damage by such agents as bleomycin (Blenoxane®; Bristol-Myers Squibb; Princeton, NJ) and anthracyclines; increased production of nucleophilic substances such as glutathione, which can compete with the target DNA for alkylation (as reflected in the acquired resistance to alkylating agents); and increased activity of DNA repair enzymes (affecting the efficacy of alkylating agents and platinum compounds) [17]. Also, hypoxia-induced changes in the expression of genes coding for oxygen-regulated proteins may result in inhibition of cell proliferation and increases in invasiveness, angiogenic potential, and drug resistance, and may thus impair treatment with chemotherapeutic agents [22]. Further, hypoxic stress proteins and loss of apoptotic potential can induce resistance to certain chemotherapeutic agents [19, 53, 54].

**Mechanisms for Beneficial Effects of rHuEPO on Radiation Therapy and Chemotherapy**

Anemia is a common condition in cancer patients that may be caused by cancer treatment (radiation therapy or chemotherapy) or by the disease itself. Clinical trials have shown that the presence of anemia can have an adverse impact on both radiation therapy and chemotherapy outcomes, including survival [55]. An apparent relationship between anemia and increased hypoxia in solid tumors has also been shown [41, 56-59], although this relationship and its clinical relevance remain controversial [25, 60-62]. Nevertheless, emerging evidence suggests that the correction of anemia may enhance the radiosensitivity and chemosensitivity of solid tumors, supporting the proposed relationship between lower hemoglobin levels and greater hypoxia [63-66]. One possible explanation for this enhancement effect is that early correction of anemia has the potential to modify the hypoxic environment of solid tumors. Degner and Sutherland, using a mathematical model of oxygen supply and oxygenation of tumor tissue, showed that increasing the hemoglobin level by 20% could produce a theoretical decrease in hypoxic tissue volume of approximately 30% [67]. Thus, correction of anemia may be a valuable strategy for oncologists to improve therapeutic and patient outcomes. Vaupel et al. have shown that the optimal hemoglobin level with regard to oxygenation status of gynecologic tumors is between 12 g/dl and 14 g/dl [59]. Another report has shown that even mild anemia may be a major causative factor for the development of hypoxia or anoxia in breast tumors [58]. In that study, the investigators developed a novel measurement, called the oxygenation gain factor (OGF), that characterized the relationship between oxygenation status and rising hemoglobin level. Using the OGF, they demonstrated that the oxygenation status of primary breast cancers depends critically on hemoglobin level. Median hemoglobin in the range of 8.5 to 14.7 g/dl correlated with exponentially greater median pO2 values (3-15 mmHg) in breast tumors. Median pO2 values in normal tissue are much higher (e.g., 51 mmHg in subcutis and 37 mmHg in skeletal muscle) and remain relatively constant over hemoglobin levels of 10-16 g/dl.

**Correcting Anemia**

One approach to correcting anemia in cancer patients is administration of recombinant human erythropoietin (rHuEPO, epoetin alfa), which elevates hemoglobin levels and

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**Table 2. Selected mechanisms for hypoxia-related tumor resistance to chemotherapy [6, 17, 18, 59]**

<table>
<thead>
<tr>
<th>Direct effects</th>
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<tbody>
<tr>
<td>• Decreased generation of free radicals, and thus, less DNA damage (bleomycin, anthracyclines)</td>
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</table>

**Indirect effects related to proteomic changes**

| • Slowing of proliferation kinetics; increase in number of cells in G0 phase |
| • G1/S-phase arrest (e.g., vinca alkaloids, methotrexate) |
| • Elevated levels of glutathione and DNA-repair enzymes (alkylating agents, bleomycin, platinum compounds) |

**Indirect effects related to genomic changes and clonal selection**

| • Loss of apoptosis and differentiation |
| • Clonal heterogeneity |
| • Proliferation of resistant clonal variants |
| • Increase in number of cells with aggressive phenotype |

**Secondary indirect effects related to intensified glycolysis with extracellular acidosis**

| • Transport of drugs across the cell membrane |
| • Intracellular drug accumulation |
| • Weak acids \( \uparrow \) (e.g., melphalan [Alkeran®; Celgene Corporation; Warren, NJ], mitomycin C [Mutamycin®; Bristol-Myers Squibb; Princeton, NJ]) |
| • Weak bases \( \downarrow \) (e.g., anthracyclines, bleomycin [Blenoxane®; Bristol-Myers Squibb; Princeton, NJ]) |
| • Drug activity |
| • \( \uparrow \) Cyclophosphamide, cisplatin (Platinol®; Bristol-Myers Squibb; Princeton, NJ), melphalan |
| • \( \downarrow \) Vinblastine (Velban®; Eli Lilly and Company; Indianapolis, IN), doxorubicin (Adriamycin®; Bedford Laboratories; Bedford, OH), bleomycin |
| • Activation of prodrugs |

**Secondary indirect effects related to chaotic angiogenesis and impact of microcirculation on intratumor pharmacokinetics**

| • Impaired and uneven drug delivery |
| • Arteriovenous shunt perfusion |
| • Large diffusion distances |
hematocrit. Several experimental and clinical studies have examined the impact of rHuEPO treatment on radiosensitivity and chemosensitivity. In a study using a tumor-associated and carboplatin-induced anemia model in rats, prevention of anemia with rHuEPO treatment resulted in a significant increase in tumor radiosensitivity, almost to the level found in nonanemic animals (Fig. 5) [68, 69]. In a similar study using a carboplatin-induced anemia model, delay in tumor regrowth after administration of cyclophosphamide was significantly shorter in the anemic group (8.6 days) than in the nonanemic control group or the group treated with rHuEPO (13.3 days) (Fig. 6) [66]. These results were interpreted as suggesting that chemotherapy-induced anemia reduces the cytotoxicity of cyclophosphamide in tumors, whereas correction of anemia with rHuEPO increases sensitivity to this agent, probably as a result of an improved oxygen supply to the tumor tissue. Silver and Piver, in a study in severe combined immunodeficient mice with engrafted human ovarian cancer, found a significantly ($p < 0.05$) greater improvement in tumor regression in the group treated with rHuEPO plus cisplatin, compared with the group treated with cisplatin only [65]. Again, the improved chemosensitivity was attributed to better oxygenation of the tumor, as a result of a higher hematocrit level. In a series of studies, Stüben et al. demonstrated that rHuEPO impacted radiosensitivity of experimental human tumors in mice [70-72]. In one study, tumor growth delay was significantly longer in animals that were protected from anemia by rHuEPO than in anemic animals [72]. Two additional studies demonstrated that anemia reduced the efficacy of radiotherapy and that rHuEPO administered to anemic mice restored radiosensitivity of experimental human tumors [70, 71].

Limited clinical trial experience using rHuEPO to prevent or correct anemia has indicated improvement in locoregional tumor control following radiation therapy [73-75] or radiochemotherapy [76]; however, extension of this research in the clinical setting is required.

CONCLUSION AND SUMMARY

Tumor hypoxia may directly contribute to the resistance of the cancer patient to radiation therapy or chemotherapy via deprivation of the oxygen essential for the cytotoxic actions of these agents. Indirectly, tumor hypoxia may contribute to radioresistance and chemoresistance by inducing proteomic and genomic changes that lead ultimately to malignant progression, with reduced local control and metastatic spread, and ultimately, increased resistance and decreased survival time. A direct association between hypoxia and anemia appears likely, and anemia is a modifiable condition in many cancer patients. This being the case, reducing tumor hypoxia by correcting anemia with rHuEPO appears to offer one possible therapeutic option for enhancing the effectiveness of standard cancer therapies. Ongoing clinical trials should help define the role of rHuEPO with respect to improvement of radiation therapy and chemotherapy. However, other strategies aimed at improving treatment sensitivity in hypoxic tumors will also have to be explored (e.g., brachytherapy, alternative radiation and chemotherapy schedules, and therapies specifically targeted at the hypoxic microenvironment) in an effort to assure optimal treatment of cancer patients.
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