**The Use of Erythropoietin in Radiation Oncology**

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Erythropoietin can minimize problems with anemia in cancer patients who receive radiation either alone or in conjunction with chemotherapy. Its use is not associated with greater thrombocytopenia or other side effects.

**Introduction**

Anemia is a common problem in patients with advanced cancer. While the etiology of anemia in cancer patients is often multifactorial, blunted erythropoietin response to anemia is considered one of the most important contributing factors in newly diagnosed cancer patients. Treatment with chemotherapy or radiotherapy or both contributes to the magnitude of anemia, which results in decreased functional capacity and quality of life. Because the efficacy of radiation therapy depends on adequate tissue oxygenation at the time of irradiation, there is continued interest in the relationship between anemia and the response to radiation therapy.

In the past, red cell transfusion -- with its associated risks, inconvenience, and cost -- was the only means to correct anemia. With the advances in molecular biologic techniques, an erythroid growth factor erythropoietin (EPO) was cloned, and recombinant human erythropoietin (rHuEpo), an erythroid growth factor, is now available for clinical use. In phase III placebo-controlled trials, EPO has been shown to increase hemoglobin levels, decrease transfusion requirements, and improve self-perceived quality-of-life parameters in anemic cancer patients undergoing chemotherapy. Taken together with the radiobiologic principle of oxygen as a critical mediator of ionizing radiation effects, it is postulated that the use of EPO during radiation therapy may improve the efficacy of radiation therapy.

Early clinical trials have proven that EPO is safe and effective in alleviating anemia during radiation therapy. Even if the EPO-induced alleviation of anemia does not result in improvement of tissue oxygenation and subsequent enhancement of therapeutic efficacy, subjective improvement in the sense of well being may motivate patients to better comply with rigorous treatment approaches such as concurrent chemoradiation therapy.

**Anemia and Radiation Therapy**

Over the past several decades, many investigators have examined the relationships between anemia and response to radiotherapy. Of 25 articles on this subject compiled by Dische in 1991, 23 reported an adverse influence of anemia on the outcome of radiotherapy. Although the cutoff value for the definition of anemia was variable, there was evidence that severe anemia, defined as hemoglobin levels of <10.0 g/dL or the requirement of blood transfusion, was associated with poor local control rates and shorter survival in patients with uterine cervical cancers and head and neck cancers. Most studies reported the same poor outcome even in patients with moderate anemia (hemoglobin levels between 10.0 and 12.0 g/dL) compared with those treated who had higher hemoglobin levels.

For example, in a series of 1,055 patients with stage IIB or III uterine cervical cancer, Bush observed that anemia during radiation therapy was associated with higher local relapse rates but not with distant metastasis rates (Table 1).

**Table 1.** Effects of Average Hemoglobin Levels During Radiotherapy on Log-Rank Adjusted Local and Distant Relapse Rates

<table>
<thead>
<tr>
<th>Hemoglobin (g/dL)</th>
<th>Number of Patients</th>
<th>Local Relapse Rate</th>
<th>Distant Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>29</td>
<td>0.46</td>
<td>0.18</td>
</tr>
<tr>
<td>10 - 11.9</td>
<td>319</td>
<td>0.29</td>
<td>0.24</td>
</tr>
<tr>
<td>12 - 13.9</td>
<td>578</td>
<td>0.20</td>
<td>0.16</td>
</tr>
<tr>
<td>&gt;=14</td>
<td>129</td>
<td>0.20</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*P value: 0.002 0.1*  

From Bush RS.

Similar findings were reported by others not only in patients with cervical cancers, but also in patients with head and cancers. In a retrospective study of 386 patients with advanced-stage IIB or III cervical cancers, for example, Girinski et al reported that a posttreatment hemoglobin level of <10.0 g/dL, but not the pretreatment hemoglobin level, was associated with a significantly higher risk of locoregional failure. Patients with at least one posttreatment hemoglobin value below the threshold of 10.0 g/dL had 1.8 times more risk of locoregional failure than those with all values above the threshold. This suggests that even relatively short periods of anemia could significantly increase the risk of locoregional failure and that hemoglobin levels at the time of radiation rather than the baseline hemoglobin values are more important to the efficacy of radiation therapy.
More recently, Tarnawski et al.18 correlated hemoglobin levels before and after radiation therapy with the probability of local tumor control in 847 patients with supraglottic squamous cell carcinomas of the larynx who were treated with radiation therapy alone. A stepwise logistic regression analysis showed that hemoglobin level at the end of radiotherapy, but not the pretreatment hemoglobin level, was the most important prognostic factor for the probability of local control. Other significant prognostic factors were T stage, overall treatment time, female sex, and age. The decrease of hemoglobin during therapy was a significant prognostic factor for local treatment failure, but it was less important than the hemoglobin level at the end of treatment. Fig 1 shows the observed cure rates according to the hemoglobin level at the end of treatment and the predicted probability of tumor control. More importantly, for the clinically observed variability range, hemoglobin level at the end of radiation therapy had a more pronounced correlation with the probability of tumor control than the overall treatment time. Although the possibility that posttreatment hemoglobin might reflect other yet unidentified prognostic factors cannot be excluded, these findings support the idea that a correlation exists between the hemoglobin level during radiation therapy and local tumor control.

Transfusion and Radiation Therapy

Investigators at the Princess Margaret Hospital in Toronto, Canada, addressed the role of anemia on radiation therapy in a randomized trial in which red blood cell transfusion was given to a group of patients with stage IIB and III cervical cancers to keep the hemoglobin levels at 13.5 g/dL or above (treatment group) vs a policy of not administering transfusions unless the hemoglobin level dropped below 10.0 g/dL (control group).4,19 In a retrospective analysis of the data, 132 patients who were prospectively enrolled in the original study19 were divided into four subgroups: (1) treatment group patients who were anemic (hemoglobin <12.5 g/dL) and given transfusions to keep hemoglobin > or = 12.5 g/dL, (2) treatment group patients with hemoglobin > or = 12.5 g/dL who were not given transfusions, (3) control group patients with hemoglobin > or = 12.5 g/dL who were not given transfusions, and (4) control group patients who were anemic (hemoglobin <12.5 g/dL) and were given transfusions only if necessary to keep hemoglobin > or = 10.0 g/dL. The log-rank was adjusted depending on stage and whether radical treatment was completed or not.4

As shown in Table 2, those patients whose hemoglobin was > or = 12.5 g/dL, either with or without transfusion, had similar local relapse rates (0.15, 0.23, and 0.21) while the control group patients who became anemic (hemoglobin <12.5 g/dL) but were transfused only if necessary to keep hemoglobin at > or = 10.0 g/dL, had the highest local relapse rate of 0.44. The difference between subgroups 1 and 4 was statistically significant (0.15 vs 0.44, P=0.0076). However, there was no significant difference in the proportion of patients dying of disease between the transfusion arm and the control arm of the study (0.35 vs 0.49, P=0.2). Obviously, the result of this retrospective analysis was not definitive in determining whether transfusion improves the local relapse rate and consequently survival of stage IIB or III cervical cancer patients. However, the data are consistent with the thesis that there is a relationship between the hemoglobin level during treatment and the probability of local relapse. It is noted that raising the hemoglobin level improved the local control rate to that of the nonanemic patients.

Table 2. – Effects of Blood Transfusions on the Log-Rank Adjusted Local Relapse Rate in 132 Patients With Stage IIB or III Cervical Cancer of the Uterus

<table>
<thead>
<tr>
<th>Transfusion Policy*</th>
<th>Group</th>
<th>Number of Patients</th>
<th>Adjusted Local Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>To keep Hb &gt; 13.5 g/dL</td>
<td>Hb &lt; 12.5 g/dL Transfused</td>
<td>38</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>Hb &gt; 12.5 g/dL Not transfused</td>
<td>28</td>
<td>0.23</td>
</tr>
<tr>
<td>To keep Hb &gt; 10.0 g/dL</td>
<td>Hb &gt; 12.5 g/dL Not transfused</td>
<td>41</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Hb &lt; 12.5 g/dL Transfused</td>
<td>26</td>
<td>0.44</td>
</tr>
</tbody>
</table>

* From Bush RS, et al.19

These results have not resolved the lingering skepticism regarding the role of anemia in the efficacy of radiation therapy. Anemia might simply reflect the presence of more advanced subset of cancer or aggressive nonresponsive tumors. Patients with advanced-stage cervical cancers were found to be more anemic than those with earlier-stage tumors. Thus, 25%, 33%, and 45% of patients with stage I, II, and III tumors, respectively, had hemoglobin levels of < 12.0 g/dL.19

Although other investigators have undertaken similar studies to assess the effects of transfusion, no other studies have convincingly demonstrated a significant improvement in radiation therapy outcome.20 The reason for this difference is not apparent, but it may in part be explained by immunosuppressive effects of blood transfusion. This notion is further supported by the results from a randomized study of autologous vs allogeneic blood transfusion in patients undergoing surgery for colorectal cancer.21 In this study of 120 patients with potentially curative resectable colorectal cancer, patients who needed allogeneic blood transfusion had a significantly higher risk of tumor recurrence compared with those who did not, with a relative risk of 6.18 (95% confidence interval, 2.20 to 17.37; P<.001). The other two independent predictors of tumor recurrence were pathological T and N stage with relative risk (95% confidence interval) of 6.61 (1.82 to 23.99; P=.004) and 8.39 (3.15 to 22.33; P<.001), respectively.21 Based on all available data, it seems prudent to balance the potential radiosensitizing effects of blood transfusion by improving oxygen-carrying capacity against the potentially deleterious effects of allogeneic blood transfusion and to look for an alternative means to improve the oxygen-carrying capacity during radiation therapy. Autologous blood transfusion is an alternative but has only limited application in cancer patients with anemia.22

Clinical Use of Erythropoietin During Radiation Therapy
Based on the premise that EPO-induced correction of anemia will increase tissue oxygenation and thereby improve the efficacy of radiation therapy, three groups have studied the effects of EPO on anemia during radiation therapy.12-14 All three trials selected the patients with hemoglobin levels below certain cutoff values, as shown in Table 3. In the first reported open-label phase II randomized trial, Vijayakumar et al12 evaluated the role of EPO in 26 patients undergoing intensive radiation therapy with or without chemotherapy for breast, lung, cervix, or prostate cancer. The study entry criteria included low hemoglobin levels (<13.0 g/dL for men and <12.0 g/dL for women). Fourteen patients were assigned to treatment with EPO (200 U/kg per day SC five times a week plus 325 mg of ferrous sulfate PO TID), and 12 patients were assigned to a control group. Mean hemoglobin values at baseline were 10.6 ± 1.6 g/dL for the control group and 11.4 ± 1.8 g/dL for the EPO group. While hemoglobin concentration declined by a mean value of 0.035 g/dL per week in the control group, it increased by 0.43 g/dL per week in the EPO-treated group.

In another randomized study, Lavey et al13 evaluated the effect of EPO in 40 patients with a hemoglobin value of <13.5 g/dL. These patients were scheduled to receive five to eight weeks of radiotherapy for a malignant tumor located above the diaphragm without evidence of distant metastasis. Twenty patients received EPO at 300 U/kg x 3, then 150 U/kg x 3 times per week SC beginning 0 to 10 days prior to the first radiation dose with oral ferrous sulfate. The remaining patients received ferrous sulfate alone and served as controls. The mean baseline hemoglobin value was 11.9 ± 2.2 g/dL and 11.8 ± 2.2 g/dL for the EPO and control group, respectively. Compared with only 5% of the controls, 80% of the EPO-treated patients achieved hemoglobin levels greater than 14 g/dL during radiation therapy. At the end of radiation therapy, the mean ± SD hemoglobin levels increased to 15.1 ± 2.2 g/dL in the EPO group while the hemoglobin levels in the control group remained stable at 11.8 ± 2.2 g/dL. No toxicity was associated with EPO use in this study.

In a third study reported by Dusenbery et al,14 20 patients with surgically staged cervical cancer and anemia (hemoglobin <12.5 g/dL) were enrolled in a phase I/II study. Fifteen were treated with EPO (200 U/kg per day) and ferrous sulfate 5 to 10 days prior to initiation of external beam radiation therapy, continuing until the hemoglobin was ≥ 14 g/dL. or radiation therapy was completed. Five were treated with ferrous sulfate alone. An additional 61 historical controls who met the eligibility criteria were analyzed. Cisplatin was given (20 mg/m² per week) as a radiosensitizer in 14 EPO patients and four concurrent control patients. In the EPO group, the mean ± SD hemoglobin rose by 30% over the course of radiation therapy (from 10.3 ± 4.0 g/dL to 13.2 ± 2.7 g/dL). The average increase in hemoglobin was 0.5 ± 1.0 g/dL per week. The average hemoglobin during radiation therapy was 13.4 ± 2.7 g/dL. In the study and historical controls, mean initial hemoglobin levels were 10.7 ± 1.4 g/dL and 11.1 ± 1.3 g/dL, respectively, which remained unchanged over the course of radiation therapy. Average hemoglobin levels during radiation therapy were 11.1 ± 1.8 g/dL in study controls and 11.4 ± 2.2 g/dL in historical controls, significantly lower than EPO-treated patients (P=0.0001). From these early trials, it is evident that EPO is both safe and effective in raising hemoglobin levels in anemic cancer patients receiving radiation therapy with or without concurrent chemotherapy with cisplatin.

<table>
<thead>
<tr>
<th>Table 3. -- Erythropoietin Trials in Radiation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
</tr>
<tr>
<td>EPO dose</td>
</tr>
<tr>
<td>Tumor types</td>
</tr>
<tr>
<td>EPO patients</td>
</tr>
<tr>
<td>Control patients</td>
</tr>
<tr>
<td>Entry Hb Criteria (g/dL)</td>
</tr>
<tr>
<td>W: &lt;12</td>
</tr>
<tr>
<td>Mean Hb at Entry (g/dL)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Hb Outcome (g/dL)</td>
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<td></td>
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</table>

* Except for one in each group, all patients also received cisplatin (20 mg/m² per week).

EPO Use During Concurrent Chemoradiation Therapy: M.D. Anderson Experience

Radiation therapy had been the treatment of choice for locally advanced inoperable non-small cell lung cancer (NSCLC) until 1990, when Dillman et al25 reported the results of the Cancer and Leukemia Group B 84-33 trial, which showed improvement in overall survival favoring combined-modality treatment (median survival = 9.7 vs 13.8 months; one-year survival = 40% vs 55%; P=0.007). These results are confirmed by the Radiation Therapy Oncology Group three-arm study (RTOG 88-08).26 Since 1990, we have investigated the concept of concurrent chemoradiation therapy, using a cisplatin and oral etoposide regimen, which showed both antitumor effects against NSCLC and radiosensitizing potential, given concurrently with hyperfractionated radiation therapy to the chest (1.2 Gy bid/total 69.6 Gy in six weeks). In a multi-institutional trial of 76 patients (RTOG 91-06),27 we observed a median survival of 18.9 months with one-year and two-year survival rates of 67% and 35%, respectively. For a subgroup of 56 patients with less than 5% weight loss, the median survival was 21.1 months with one-year and two-year survival rates of 70% and 42%, respectively. This concurrent chemoradiation therapy strategy was further explored in subsequent RTOG 92-04 (arm 2)28 and RTOG 94-10 (arm 3) trials with a
minor modification of the regimen. To avoid excessive toxicity, the duration of oral etoposide administration was reduced from 14 days to 10 days given only on the day of radiation therapy over the first two-week period of each cycle.

In contrast to previous experience with chest radiation alone, the addition of chemotherapy to chest radiation produced significant anemia in most patients. Of 18 patients who were enrolled for RTOG 92-04 from our institution, anemia defined as hemoglobin levels of <12 g/dL in women and <13 g/dL in men was noted in 89% of 18 patients during concurrent chemoradiation. Moreover, the nadir hemoglobin value was less than 10 g/dL in 7 (39%) of 18 patients after the first course and in 15 (83%) of 18 patients over the entire treatment course (unpublished data). The average drop in hemoglobin was 4.0 g/dL (range = 2.3 to 7.1 g/dL), and 78% of the patients had a greater than 3.0 g/dL decrease from the baseline pretherapy value.

DM 95-186: TREATMENT PLAN

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>RTOG 94-10 Without EPO</th>
<th>DM 95-186 With EPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>16 (9M / 7F)</td>
<td>16 (11M / 5F)</td>
</tr>
<tr>
<td>Median hemoglobin (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretherapy</td>
<td>13.2 (10.9 - 15.0)</td>
<td>13.2 (11.9 - 16.1)</td>
</tr>
<tr>
<td>Nadir</td>
<td>9.5 (6.5 - 13.7)</td>
<td>11.5 (9.0 - 15.8)</td>
</tr>
<tr>
<td>Difference</td>
<td>3.3 (1.2 - 7.5)</td>
<td>1.5 (+0.4 - 5.6)</td>
</tr>
<tr>
<td>Days to nadir</td>
<td>42 (21 - 98)</td>
<td>35 (16 - 79)</td>
</tr>
</tbody>
</table>

Conclusions

With these data as a background, a phase II single-arm trial was initiated to evaluate the efficacy and safety of EPO in this concurrent chemoradiation setting (Fig 2). The treatment schedule is basically the same as arm 2 of RTOG 92-04 protocol25 and also arm 3 of the concurrently ongoing RTOG 94-10 protocol. This trial differed from the other two trials in two aspects: (1) EPO 10,000 U/kg was given subcutaneously 3 times a week for 12 weeks, and (2) patients with weight loss > or = 5% were allowed. Also, unlike other EPO trials,12-14 all patients were required to have a relatively normal hemoglobin level of > or = 12.0 g/dL, and the main study endpoint was to maintain the hemoglobin levels close to normal using 10 g/dL as a cutoff value. Less than 10 g/dL hemoglobin means grade II or greater anemia.

Initially, we did not intend to give iron supplements. However, on observing a significant drop in hemoglobin values in the first four patients, the protocol was revised to give 325 mg of ferrous sulfate orally three times a day throughout the 12-week period of EPO administration. This change in iron supplement policy had a dramatic effect on the magnitude of anemia, as shown in Table 4. To date, 19 patients have been enrolled in this trial of chemoradiation plus EPO. Hematologic toxicity was evaluated in 16 patients. The results from these 16 patients are compared with the data obtained from 16 patients who were enrolled in arm 3 of the RTOG 94-10 protocol, who basically received the same treatment but without the benefit of EPO and iron supplement. The median hemoglobin value at study entry was 13.2 g/dL for both groups. With EPO, the nadir hemoglobin value was significantly higher than without EPO (11.5 g/dL vs 9.5 g/dL) with the median drop in hemoglobin of 1.5 g/dL vs 3.3 g/dL, favoring the EPO-treated group.26 When the patients who were given both EPO and iron supplements were analyzed separately, this group of 12 patients had even better results, as shown in Fig 3. While the baseline hemoglobin values are basically the same (13.2 g/dL), EPO plus iron supplement significantly reduced the degree of anemia (median nadir hemoglobin = 11.8 vs 9.5 g/dL; grade II or greater anemia = 1/12 [8%] vs 9/16 [56%]) and the requirement for blood transfusion (1/12 [8%] vs 6/16 [37.5%]) compared with the patients treated without EPO or iron supplement (RTOG 94-10, arm 3). With EPO alone, median nadir hemoglobin was 9.7 g/dL, and two of four patients developed grade II or greater anemia, but none received transfusion. No other significant side effects were noticed. More specifically, EPO did not cause thrombocytopenia, a toxicity that has been reported when other growth factors such as GM-CSF were given concurrently with chemoradiation therapy.27 Based on these preliminary results, we recommend iron supplements in patients receiving EPO, even in the absence of clinical signs of iron deficiency.
Anemia and anemia-associated tissue hypoxia are critically important for the efficacy of radiation therapy. The results from prior studies, as well as those from our ongoing study, indicate that EPO is safe to administer, even with concurrent chemoradiation therapy, and it also is effective in maintaining the hemoglobin levels above a threshold level. In addition, it also reduces transfusion requirements and has improved the self-reported quality-of-life parameters. In the past, blood transfusion has been considered a useful adjuvant to radiation therapy based on the premise that higher hemoglobin levels would improve tissue oxygenation and thereby enhance the efficacy of radiation therapy. However, this premise has not been clinically confirmed. Whether the EPO-induced effects on hemoglobin and improvement in oxygen-carrying capacity will translate into improvement in overall efficacy of chemoradiation therapy remains to be studied in a large, prospectively randomized trial.

Compared with red cell transfusion, EPO provides an opportunity to assess the role of anemia in radiation therapy without the confounding effect of transfusion-induced immunosuppression. A prospective, randomized trial of EPO is warranted in patients undergoing intensive combined chemoradiation therapy for locally advanced inoperable NSCLCs or stage IIB or III cervical cancers.

References


**DR HORTON**

Was there any difference in the incidence of esophagitis in the erythropoietin-treated vs the nontreated groups?

**DR LEE**

Even though overall tolerance in the erythropoietin-treated patients improved, the rate of esophagitis seemed similar.

**DR HORTON**

My experience with patients receiving concomitant chemotherapy and radiation for lung cancer is based on those I see in the inpatient service. Esophagitis can be severe in these patients. Theoretically, one could argue that erythropoietin should enhance the vascularity of the normal esophagus as well as of the tumor and therefore you might be enhancing radiation reaction in the esophagus as well as against the tumor.

**DR LEE**

That was a concern we had, because when radiosensitizers are used, normal tissue is radiosensitized as well as the tumor. However, the positive effect of correcting anemia was so overwhelming that patients would tolerate small increases in esophagitis or other toxicities.

**DR DALTON**

When did the anemia occur in these patients with concurrent chemotherapy and radiation, and when did patients reach their nadir?

**DR LEE**

The nadir of anemia occurred at a median of approximately 42 days, during or immediately before the end of treatment with radiation therapy and the second course of chemotherapy. We usually give a second course of chemotherapy at approximately day 29, and the nadir occurred about 14 days after the second course.

**DR ZUCKERMAN**

About 10 years ago at the University of Alabama, we were one of the largest centers participating in the original study in EPO in renal failure. At that time, we expected virtually 100% of these patients to respond to EPO. Early in the study, we learned that a small group did not respond. When we studied the iron studies, we found that there is a cutoff in a non-iron deficient range of a transferrin saturation of about 20% and of a ferritin level of about 100 below which there is an increased proportion of people who do not respond optimally to EPO. We began to monitor iron studies closely and to administer iron to whomever fell below those cutoff numbers.

We also observed an interesting effect regarding erythropoietin response during the course of that study. In our own group of approximately 45 patients at the University of Alabama, one developed pancreatitis, one broke her hip, three or four were admitted to the hospital with pneumonia or sepsis, and six required shunt revisions. Without exception, these patients shut down erythropoiesis completely despite receiving stable levels of EPO. As soon as the episode was over, they started responding once again to the same doses of EPO they were taking before.

**DR BENNETT**

AIDS-related malignancies provided our first clue that EPO was beneficial. The endogenous EPO level was clearly related to response. So now there are at least two models in which the lower the serum EPO level, the more likely a response will occur.

**DR SABA**

Since carboplatin has considerable myelotoxicity but cisplatin has less, why do cisplatin-treated patients develop more anemia, especially without azotemia?

**DR BENNETT**

Anemia is one of the most common hematopoietic side effects of cisplatin. In some cases, decreased production of erythropoietin seems to be independent of renal function, but I think that is anecdotal. About 15 years ago, some reports suggested that cisplatin could act like a heavy metal and cause a kind of sideroblastic anemia, but again, that was anecdotal. I do not know if any studies have investigated that problem.

**DR SPIVAK**

Two studies suggested that cisplatin may not directly act on the erythroid progenitor cell. Another study, from Albany, showed that there was a more substantial effect on the kidney than suspected. You can dissect the endocrine and the exocrine function of the kidney, especially in diabetics, and show that patients who have minimal creatinine elevations have lost the relationship between hemoglobin and erythropoietin. This is an effect that could be missed in clinical biochemical testing.
It is not commonly known, but a study was done, I believe in Japan, showing that the DNA adducts caused by cisplatin persisted longer in older people than in younger people. So there may be some selective toxicity as well.

I am unaware of any studies addressing this, but people who receive cisplatin develop anemia quickly, too fast to account for it on the basis of even ceasing all bone marrow function. That indicates that there has to be either hemolysis or a dilutional effect.

What is the effect of cisplatin on erythropoietin release? My feeling is that erythropoietin is shut down quickly, followed by a drop in hemoglobin.

It can’t be just a shutdown of erythropoietin; that is a longer-term effect. As Dr Spivak noted, if you could abolish all erythropoietin activity today, you would not notice anemia in these people a week from today, based on the lifespan of the red cell. In 12 days, you would lose only 10% of red cell mass.

We’re talking about the effects of chemotherapeutic drugs on red cells in anemia. I’d like to address the converse: the influence of anemia on the effect of cytotoxic drugs, principally considering their pharmacokinetics. In an Italian study done in the early 80s with doxorubicin, patients who were anemic at the time of drug administration had more profound myelosuppression compared with those who were not anemic. Many drugs do, in fact, bind to red cells. David Alberts at Arizona showed that mitoxantrone and anthracycline binds significantly to red cells, which will change the free amount -- the drug-free availability -- and might possibly increase toxicity. The bottom line is that if you have anemic patients, you might want to administer transfusions before giving the chemotherapy rather than treating them while they are profoundly anemic.