Chemotherapy-Induced Anemia in Adults: Incidence and Treatment

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Anemia is a common complication of myelosuppressive chemotherapy that results in a decreased functional capacity and quality of life (QOL) for cancer patients. Severe anemia is treated with red blood cell transfusions, but mild-to-moderate anemia in patients receiving chemotherapy has traditionally been managed conservatively on the basis of the perception that it was clinically unimportant. This practice has been reflected in the relative inattention to standardized and complete reporting of all degrees of chemotherapy-induced anemia. We undertook a comprehensive review of published chemotherapy trials of the most common single agents and combination chemotherapy regimens, including the new generation of chemotherapeutic agents, used in the treatment of the major nonmyeloid malignancies in adults to characterize and to document the incidence and severity of chemotherapy-induced anemia. Despite identified limitations in the grading and reporting of treatment-related anemia, the results confirm a relatively high incidence of mild-to-moderate anemia. Recent advances in assessing the relationships of anemia, fatigue, and QOL in cancer patients are providing new insights into these closely related factors. Clinical data are emerging that suggest that mild-to-moderate chemotherapy-induced anemia results in a perceptible reduction in a patient's energy level and QOL. Future research may lead to new classifications of chemotherapy-induced anemia that can guide therapeutic interventions on the basis of outcomes and hemoglobin levels. Perceptions by oncologists and patients that lesser degrees of anemia must be endured without treatment may be overcome as greater emphasis is placed on the QOL of the oncology patient and as research provides further insights into the relationships between hemoglobin levels, patient well-being, and symptoms. [J Natl Cancer Inst 1999;91:1616–34]

Although correction of severe anemia in patients undergoing chemotherapy requires red blood cell (RBC) transfusions, mild-to-moderate anemia in patients receiving chemotherapy for nonmyeloid malignancies has traditionally been managed conservatively, with little consideration of its impact on patient well-being *(1)*. Until the early 1980s, RBC transfusions—which were usually administered empirically when hemoglobin concentrations declined below 10 g/dL *(2,3)*—were the primary treatment of cancer-related anemia, including chemotherapy-induced anemia; however, concern about the safety of the blood supply, related to potential transmission of the human immunodeficiency virus (HIV), prompted clinicians to alter their treatment approach *(4)*. With no alternative to transfusion, treatment of mild-to-moderate anemia was generally avoided; intervention was withheld until hemoglobin concentrations declined to more severe levels (i.e., 7–8 g/dL) or the patient experienced signs and symptoms of severe anemia *(2,5)*. As a consequence, the perception developed that anemia that did not reach the transfusion trigger point was clinically unimportant in otherwise uncompromised patients. These factors likely contributed to a tendency for anemia and its management to receive less attention in published chemotherapy trials and in the literature.

New data are emerging that demonstrate that chemotherapy-induced anemia (including mild-to-moderate anemia) has an adverse impact on quality of life (QOL) that can be improved with epoetin alfa treatment *(6–8)*. With the introduction of a new generation of promising chemotherapeutic agents, such as the taxanes and camptothecins, there has been rapid evolution of chemotherapy treatments and regimens for many of the major tumors. In this context, we reviewed the incidence and severity of anemia in adults associated with both traditional and new chemotherapy regimens and the management of chemotherapy-related anemia.

Assessing Chemotherapy-Induced Anemia and Its Impact

Anemia is common in patients with cancer and is a frequent complication of myelosuppressive chemotherapy. The severity of anemia depends on the extent of disease and the intensity of treatment. Repeated cycles of chemotherapy may impair erythropoiesis cumulatively. The symptoms of anemia can reduce QOL. The most common patient complaints are fatigue and dyspnea on exertion, which can have adverse effects on a patient's ability to perform normal daily activities. Because QOL is gaining greater importance in evaluating outcomes of patient care and new clinical research has better characterized the relationship between anemia and QOL, perceptions and attitudes regarding the treatment of anemia, particularly degrees of anemia that have been considered of lesser clinical importance or necessary for patients to tolerate to avoid transfusions, require reassessment.

The National Cancer Institute (NCI) and the World Health Organization (WHO) toxicity criteria, two of the most commonly used standard criteria for the assessment of therapy-induced toxicity, are the same in their classification of more severe grades of anemia (grade 3, 6.5–7.9 g of hemoglobin/dL; grade 4, <6.5 g of hemoglobin/dL) but differ slightly in their

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classification of lesser grades (Table 1). The major cooperative groups in the United States also have their own toxicity grading criteria for anemia, which are similar or identical to the NCI Common Toxicity Criteria, i.e., grade 1 (mild), 10.0 g hemoglobin/dL to within normal limits; grade 2 (moderate), 8.0–10.0 g of hemoglobin/dL; grade 3 (serious or severe), 6.5–7.9 g of hemoglobin/dL; and grade 4 (life threatening), less than 6.5 g of hemoglobin/dL. Only in this decade has there been a substantial increase in the use of these standardized toxicity grading systems in chemotherapy evaluation and reporting. In addition, numerous reports in the literature fail to specify the toxicity grading system used, report anemia in terms of decreases in hemoglobin levels rather than by grade, or even omit information on the incidence or severity of anemia. As a result, it can be difficult to fully characterize and directly compare toxicity across different regimens and different trials as reported in the literature. The lack of treatment options for lesser degrees of anemia, coupled with the perceived relative clinical importance of other cytopenias (i.e., neutropenia or thrombocytopenia), likely contributed to the reduced attention to standardized and complete reporting of all degrees of chemotherapy-related anemia.

Unfortunately, none of the standard toxicity grading systems, including the WHO and NCI toxicity criteria, are capable of clearly relating anemia, as measured by a numeric gradient in hemoglobin, to clinical symptomatology or to the patient's well-being. Evaluating fatigue, one of the cardinal symptoms of anemia, presents additional problems. Fatigue is the most frequently reported symptom in cancer patients, affecting an estimated 80% to almost 100% of the patients receiving anticancer therapy *(9–11)*. Despite its high prevalence, fatigue is seldom discussed by patients and their oncologists, and it is infrequently treated *(10,12)*. Fatigue can be physically and emotionally distressing to patients, causing some to withdraw from potentially curative treatment *(13)*. Of all anemia-related symptoms, fatigue appears to exert the greatest adverse impact on QOL. However, it has been difficult to quantify the relationship between anemia and fatigue in the cancer population, in part because of these conditions' multifactorial causes and the lack of an instrument to assess the full spectrum of anemia-related symptoms.

Yellen et al. *(14)* recently developed and validated two new survey instruments that measure the impact of fatigue and other anemia-related symptoms in patients with cancer: 1) the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) scale, which contains a specific fatigue subscale, and 2) the FACT-Anemia (FACT-An), which contains the FACT-F plus questions related to anemia but unrelated to fatigue. With the use of these scales, it was possible to reliably discriminate patients on the basis of hemoglobin level and Eastern Cooperative Oncology Group performance status; the fatigue subscale and the nonfatigue items of the FACT-An also differentiated patients by these two measures. Higher hemoglobin levels were associated with less fatigue and better QOL. These scales have been proven to be reliable and valid measures of QOL in cancer patients, with particular focus on anemia and fatigue.

Cella et al. *(6,15)* used the FACT-An instrument to assess the impact of anemia and fatigue on QOL in 50 patients with a variety of malignancies who had hemoglobin levels determined within 48 hours before assessment and who were not currently receiving radiotherapy. Patients with hemoglobin levels greater than 12 g/dL reported statistically significantly less fatigue ($P = .01$), fewer nonfatigue anemia symptoms ($P = .02$), better physical ($P = .003$) and functional ($P = .001$) well-being, and higher overall QOL ($P = .003$) than those with hemoglobin levels less than or equal to 12 g/dL. To further evaluate the effect of hemoglobin levels on QOL, a multiple regression analysis was performed in which fatigue was removed as a variable. Statistically significant hemoglobin effects on ability to work ($P = .005$), leisure activities ($P = .03$), and overall QOL ($P = .001$) remained. Of the nonfatigue symptoms of anemia, dizziness accounted for the greatest functional difficulty. These results confirmed the impact of anemia-related fatigue and other symptoms on QOL in cancer patients.

Langer et al. *(16)* recently evaluated the effect of chemotherapy-induced anemia on QOL in patients with advanced non-small-cell lung cancer (NSCLC) by use of an index based on FACT-Lung subscales that measure physical and functional well-being plus symptoms specific to lung cancer. The incidence of at least grade 2 anemia was cumulative, increasing from 30% after the first cycle of treatment to 59% by the fourth cycle. A statistically significant correlation ($r = .38$; $P \leq .02$), which was independent of tumor response status, was demonstrated between worsening anemia and declining QOL by the fourth cycle of chemotherapy.

Incidence and Severity of Chemotherapy-Induced Anemia in Selected Nonmyeloid Malignancies

The incidence and severity of chemotherapy-related anemia depend on a variety of factors, including the type, schedule, and

Table 1. Grading systems for anemia*

Severity	Toxicity grading system					
	WHO	NCI	ECOG	SWOG	CALGB	GOG
Grade 0 (WNL)†	≥11.0 g/dL	WNL	WNL	WNL	WNL	WNL
Grade 1 (mild)	9.5–10.9 g/dL	10.0 g/dL to WNL	10.0 g/dL to WNL	10.0 g/dL to WNL	10.0 g/dL to WNL	10.0 g/dL to WNL
Grade 2 (moderate)	8.0–9.4 g/dL	8.0–10.0 g/dL	8.0–10.0 g/dL	8.0–9.9 g/dL	8.0–10.0 g/dL	8.0–10.0 g/dL
Grade 3 (serious/severe)	6.5–7.9 g/dL	6.5–7.9 g/dL	6.5–7.9 g/dL	6.5–7.9 g/dL	6.5–7.9 g/dL	6.5–7.9 g/dL
Grade 4 (life threatening)	<6.5 g/dL	<6.5 g/dL	<6.5 g/dL	<6.5 g/dL	<6.5 g/dL	<6.5 g/dL

*WHO = World Health Organization; NCI = National Cancer Institute; ECOG = Eastern Cooperative Oncology Group; SWOG = Southwest Oncology Group; CALGB = Cancer and Leukemia Group B; GOG = Gynecologic Oncology Group; WNL = within normal limits.

†WNL hemoglobin values are 12.0–16.0 g/dL for women and 14.0–18.0 g/dL for men.

intensity of therapy administered and whether the patient has received prior myelosuppressive chemotherapy, radiation therapy, or both. Symptom severity depends on the degree of anemia, the type of underlying malignancy, and the patient's pulmonary and cardiovascular function *(17)*. Elderly cancer patients frequently manifest clinical symptoms of anemia at higher hemoglobin levels than do anemic patients without cancer. These factors must be considered in evaluating the toxicity data of individual chemotherapeutic agents or combination chemotherapy regimens. In addition to previously identified limitations associated with the grading and reporting of treatment-related anemia, published clinical trial reports in oncology tend to focus greater attention on the most severe toxic effects, sometimes incompletely reporting details on the incidence of lower grades of toxic effects. This reporting is potentially important for lesser degrees of anemia, because these degrees are being recognized to cause a perceptible reduction in a patient's energy level and QOL.

Retrospective reviews of the incidence of anemia that required RBC transfusions in patients with nonmyeloid malignancies who received cytotoxic chemotherapy indicate that the highest frequency occurs in those patients with lymphomas, lung tumors, and gynecologic (ovarian) or genitourinary tumors *(18–20)* in which the incidence may be as high as 50%–60% *(17)*. In an audit of 28 oncology centers in the U.K. involving 2821 patients with solid tumors, 33% of the patients required at least one transfusion (range, from 19% for breast cancer to 43% for lung cancer) and 16% required multiple transfusions *(18)*. The proportion of anemic (hemoglobin <11 g/dL) patients increased from 17% before the first chemotherapy cycle to 35% by the sixth cycle of treatment, with 49% and 51% of the patients with ovarian and lung tumors, respectively, anemic by the sixth cycle of chemotherapy. The mean hemoglobin concentration at which a transfusion was given decreased progressively with the treatment cycle.

To document the incidence of chemotherapy-related anemia associated with the most common single chemotherapeutic agents and combination chemotherapy regimens, including newer chemotherapeutic agents and evolving combination regimens used in the treatment of the major nonmyeloid malignancies in adults, we reviewed the literature published between 1990 and 1998. We identified the most commonly recommended chemotherapies for these tumors from multiple authoritative sources, including DeVita et al. *(21)* and Greco *(22)*. In addition, The Medical Letter's Drugs of Choice for Cancer Chemotherapy *(23)* and available American Society of Clinical Oncology *(24)* and National Comprehensive Cancer Network guidelines *(25–32)* were consulted. Publications from the reference lists of these sources on phase II and III trials of the recommended chemotherapies were identified and retrieved. (For a few regimens, it was necessary to identify references published before 1990 to document reported anemia.) In addition, MEDLINE® searches were performed to identify phase II and III trials of new chemotherapy agents introduced during this decade (i.e., taxanes—docetaxel and paclitaxel; gemcitabine; vinorelbine; camptothecins—irinotecan and topotecan); this search was supplemented with manual searches of the Proceedings of the American Society of Clinical Oncology for 1994–1998. Only English-language publications reporting the incidence of the degrees of anemia were included. The chemotherapy regimen dose and schedule, previous treatment for metastatic disease, number of evaluable patients, incidence and severity of anemia, and toxicity grading system were specified (Tables 2–8).

Non-Small-Cell Lung Cancer

Platinum-based combination chemotherapy is recommended as first-line treatment for advanced NSCLC *(22–24,29)*. Because platinum is a mainstay in the treatment of lung cancer, patients with this disease commonly experience clinically important decreases in hemoglobin. In a study of 124 patients with NSCLC, a statistically significant inverse relationship was found between the accumulated dose of cisplatin and the lowest nadir of hemoglobin ($P = .04$) *(33)*. Survival of the patients who required transfusion after chemotherapy was statistically significantly shorter than that of the patients not requiring transfusion ($P<.05$; Wilcoxon–Gehan test).

Chemotherapy with paclitaxel–platinum is one of the most active regimens available for the treatment of NSCLC *(16,34–36)*. Paclitaxel–carboplatin produces an objective response rate of approximately 50%, 1-year survival rates ranging from 32% to 54%, and a median survival of at least 1 year in advanced-stage NSCLC patients *(16,34–36)*. The addition of carboplatin or cisplatin to paclitaxel results in a slight increase in grade 3 or 4 anemia compared with paclitaxel alone in previously untreated patients with advanced disease (Table 2, A) *(34,49–52)*. Paclitaxel–carboplatin produced grade 3 or 4 anemia in 5%–7% of the patients *(49)*, and paclitaxel–cisplatin produced grade 3 or 4 anemia in 5%–23% of the patients with advanced NSCLC *(50–52)*; the incidence of grade 3 or 4 anemia increased to 34% when the more myelosuppressive 24-hour paclitaxel infusion was combined with carboplatin dosed by the Calvert formula to an area under the concentration-versus-time curve of 7.5 *(36)*.

Vinorelbine–cisplatin is also a regimen for the treatment of advanced NSCLC. In a phase III trial of vinorelbine–cisplatin, 24% of previously untreated patients with advanced NSCLC experienced grade 3 or 4 anemia *(57)*. An older regimen used more widely outside the United States (i.e., mitomycin C–vinblastine–cisplatin) produced grade 1 or 2 anemia and grade 3 or 4 anemia in 61% and 9% of patients with NSCLC, respectively *(58)*. Combination regimens of etoposide–cisplatin and gemcitabine–cisplatin produced grade 3 or 4 anemia in 42% and 13%–28% of previously untreated patients with NSCLC, respectively; milder degrees of anemia were not reported in these trials *(53,55,56)*.

Numerous phase II studies have evaluated newer agents, such as the taxanes—paclitaxel and docetaxel—as well as vinorelbine and gemcitabine in previously untreated patients with advanced NSCLC. In general, these new agents are associated with high incidences of grade 1 or 2 anemia and low incidences of grade 3 or 4 anemia (Table 2, A). Single-agent paclitaxel produced little grade 3 or 4 anemia (0%–5%) in previously untreated patients with NSCLC when administered over 3 or 24 hours *(37–39)*; grade 1 or 2 anemia occurred in 23%–47% of the patients with a 3-hour paclitaxel infusion duration *(37,38)* and in 100% of the patients with a 24-hour infusion duration *(39)*. Docetaxel produced grade 1 or 2 anemia in 73%–85% and grade 3 or 4 anemia in 2%–10% of previously untreated patients with advanced NSCLC *(40–42)*. Vinorelbine produced low incidences of grade 3 or 4 anemia (1%–8%) in previously untreated patients with advanced disease but high incidences of grade 1 or 2 anemia (48%–75%) *(47,48)*. Similar incidences of grade 1 or 2 anemia (8%–69%) and grade 3 or 4 anemia (2%–5%) have

Table 2. Chemotherapy-induced anemia: lung cancer*

Treatment	Study/type (reference No.)	Regimen	No. of evaluable patients	Anemia,† % of patients	
				Grade 1 or 2	Grade 3 or 4
		A. Advanced non-small-cell lung cancer			
Single agent					
Previously untreated patients					
Paclitaxel	Ranson et al., 1997/phase II *(37)*	200 mg/m^2 3-h IV; cycles repeated every 21 d	21	23‡	5 (grade 3)‡
	Millward et al., 1996/phase II *(38)*	200 mg/m^2 3-h IV; cycles repeated every 21 d	51	47‡	0‡
	Murphy et al., 1993/phase II *(39)*	200 mg/m^2 24-h IV; cycles repeated every 21 d	25	100‡	0‡
Docetaxel	Miller et al., 1995/phase II *(40)*	75 mg/m^2 1-h IV; cycles repeated every 21 d	20	85	10
	Francis et al., 1994/phase II *(41)*	100 mg/m^2 1-h IV; cycles repeated every 21 d	29	79	6
	Fossella et al., 1994/phase II *(42)*	100 mg/m^2 1-h IV; cycles repeated every 21 d	41	73	2
Gemcitabine	Anderson et al., 1994/phase II *(43)*	800–1000 mg/m^2 30-min IV on d 1, 8, and 15; cycles repeated every 28 d	81	69‡	5‡
	Stadler et al., 1997/phase II *(44)*	1200 mg/m^2 30-min IV on d 1, 8, and 15; cycles repeated every 28 d	39	8‡	2 (grade 3)‡
	Gatzemeier et al., 1996/phase II *(45)*	1250 mg/m^2 30-min IV on d 1, 8, and 15; cycles repeated every 28 d	161	63‡	5‡
Vinorelbine	O'Rourke et al., 1993/phase II *(46,47)*	30 mg/m^2 IV weekly	143	76‡	1‡
	Vokes et al., 1995/phase II *(48)*	80 mg/m^2 PO weekly§	124	48	8
		100 mg/m^2 PO weekly§	27	55	0
Combination therapy					
Previously untreated patients					
Paclitaxel–carboplatin	Kosmidis et al., 1997/phase III *(49)*	Pac: 175 mg/m^2 3-h IV Carbo: AUC 6 IV Cycles repeated every 21 d	16	10‡	7 (grade 3)‡
		Pac: 225 mg/m^2 3-h IV Carbo: AUC 6 IV Cycles repeated every 21 d	12	25‡	5 (grade 3)‡
	Langer et al., 1995/phase II *(36)*	Pac: 135 mg/m^2 24-h IV on d 1 Carbo: AUC 7.5 IV on d 2 G-CSF: 5 μg/kg on d 3–17 Cycles repeated every 21 d	53	59‡	34‡
Paclitaxel–cisplatin	Pirker et al., 1995/phase II *(50)*	Pac: 175 mg/m^2 3-h IV Cis: 50 mg/m^2 IV on d 1 and 2 Cycles repeated every 21 d	20	60‡	5‡
	von Pawel et al., 1996/phase II *(51)*	Pac: 175 mg/m^2 3-h IV Cis: 75 mg/m^2 1-h IV Cycles repeated every 21 d	328‖	45‖	5‖
	Postmus et al., 1996/phase II *(52)*	Pac: 175 mg/m^2 3-h IV Cis: 80 mg/m^2 IV Cycles repeated every 21 d	35	NR	23‡
Etoposide–cisplatin	Miller et al., 1995/phase II *(53)*	Etop: 50 mg/m^2 PO on d 1–21 Cis: 100 mg/m^2 IV Cycles repeated every 28 d	60	NR	42
	Robert et al., 1994/phase II *(54)*	Etop: 50 mg/m^2 PO on d 1–21 Cis: 30–33 mg/m^2 20-min IV on d 1, 8, and 15 Cycles repeated every 28 d	59‖	73‖	20‖
Gemcitabine–cisplatin	Shepherd et al., 1997/phase II *(55)*	Gem: 1500 mg/m^2 IV on d 1, 8, and 15 Cis: 30 mg/m^2 IV on d 1, 8, and 15 Cycles repeated every 28 d	39	NR	28‡
	Abratt et al., 1997/phase II *(56)*	Gem: 1000 mg/m^2 IV on d 1, 8, and 15 Cis: 100 mg/m^2 IV on d 15 Cycles repeated every 28 d	50	NR	13.4‡
Vinorelbine–cisplatin	Wozniak et al., 1998/phase III *(57)*	Vino: 30 mg/m^2 20-min IV weekly Cis: 120 mg/m^2 1-h IV on d 1 and 29 then every 6 wk	204	NR	24‡
Mitomycin C–vinblastine–cisplatin (MVP)	Ellis et al., 1995/phase II *(58)*	Mit: 8 mg/m^2 IV¶ Vin: 6 mg/m^2 IV Cis: 50 mg/m^2 IV Cycles repeated every 21 d	113	61‡	9‡

(Table continues)

Table 2 (continued). Chemotherapy-induced anemia: lung cancer*

Treatment	Study/type (reference No.)	Regimen	No. of evaluable patients	Anemia,† % of patients	
				Grade 1 or 2	Grade 3 or 4
Vinblastine–cisplatin	Kosty et al., 1994/phase III *(59)*	Vin: 5 mg/m^2 IV every 7 d Cis: 100 mg/m^2 every 28 d	131	NR	13‡
		B. Advanced small-cell lung cancer			
Single agent					
Previously untreated patients					
Paclitaxel	Ettinger et al., 1995/phase II *(61)*	250 mg/m^2 24-h IV Cycles repeated every 21 d	34	0#	0#
Topotecan	Schiller et al., 1996/phase II *(62)*	1.5 mg/m^2 30-minute IV on d 1–5 Cycles repeated every 21 d	13	NR	15 (grade 3)§
		1.5 mg/m^2 30-min IV on d 1–5 G-CSF: 5 μg/kg for 10–14 d starting on d 6 Cycles repeated every 21 d	35	NR	32‡
Previously treated patients					
Docetaxel	Smyth et al., 1994/phase II *(63)*	100 mg/m^2 1-h IV Cycles repeated every 21 d	34	60‡	3 (grade 3)‡
Vinorelbine	Jassem et al., 1993/phase II *(64)*	30 mg/m^2 20-min IV every 7 d	25	40 (grade 1)‡	4 (grade 3)‡
	Furuse et al., 1994/phase II *(65)*	25 mg/m^2 IV every 7 d	24	50‡	21 (grade 3)‡
Topotecan	Ardizzoni et al. 1997/phase II *(66)*	1.5 mg/m^2 30-min IV on d 1–5 Cycles repeated every 21 d	403#	87‖	12‖
Combination therapy					
Previously untreated patients					
Cisplatin–etoposide	Hainsworth et al., 1995/phase II *(67)*	Cis: 20 mg/m^2 IV on d 1–5 Etop: 80 mg/m^2 IV on d 1–5 Cycles repeated every 21 d	60	NR	35‡
	Loehrer et al., 1995/phase III *(68)*	Cis: 20 mg/m^2 IV on d 1–4 Etop: 100 mg/m^2 IV on d 1–4 Cycles repeated every 21 d	82	NR	16‡
	Miller et al., 1995/phase III *(69)*	Cis: 25 mg/m^2 IV on d 1–3 Etop: 130 mg/m^2 IV on d 1–3 Cycles repeated every 21 d	156	NR	32**
	Skarlos et al., 1994/phase III *(70)*	Cis: 33 mg/m^2 IV on d 1–3 Etop: 50 mg/m^2 PO on d 1–21 Cycles repeated every 28 d	150	NR	55‡
		Cis: 50 mg/m^2 IV on d 1–2 Etop: 100 mg/m^2 IV on d 1–3 Cycles repeated every 21 d	71	59‡	NR
Carboplatin–etoposide	Luikart et al., 1993/phase II *(71)*	Carbo: 125-mg/m^2 on d 1–3 Etop: 200 mg/m^2 on d 1–3 Cycles repeated every 28 d	48	NR	54**
	Skarlos et al., 1994/phase III *(70)*	Carbo: 300 mg/m^2 Etop: 100 mg/m^2 on d 1–3 Cycles repeated every 21 d	72	39‡	NR
Cyclophosphamide–doxorubicin–vincristine (CAV)	Figueredo et al., 1985/phase II *(72)*	Cyclo: 990 mg/m^2 Dox: 50 mg/m^2 Vinc: 1 mg/m^2	51	13 (grades 1–4)‡	NR
		Cyclo: 1560 mg/m^2 Dox: 59 mg/m^2 Vinc: 0.9 mg/m^2	52	54 (grades 1–4)‡	NR
Ifosfamide–carboplatin–etoposide (ICE)	Wolff et al., 1995/phase II *(73)*	Ifo: 3.75 g/m^2 24-h IV with mesna Carbo: 300 mg/m^2 IV Etop: 50 mg/m^2 PO daily for 14 d Cycles repeated every 28 d	17	77#	6 (grade 3)#
		Ifo: 5 g/m^2 24-h IV with mesna Carbo: 300 mg/m^2 IV Etop: 50 mg PO daily for 21 d Cycles repeated every 28 d	18	78‡	11 (grade 4)‡
Etoposide–ifosfamide–cisplatin (VIP)	Miller et al., 1995/phase III *(69)*	Etop: 50 mg/m^2 IV on d 1–4 Ifo: 1.2 g/m^2 IV on d 1–4†† Cis: 20 mg/m^2 IV on d 1–4 Cycles repeated every 21 d	80	NR	52‡
	Faylona et al., 1995/phase II *(74)*	Etop: 37.5 mg/m^2 PO daily on d 1–21 Ifo: 1.2 g/m^2 IV on d 1–4§§ Cis: 20 mg/m^2 IV on d 1–4 Cycles repeated every 28 d	22	NR	23 (grade 3)‡‡

(Table continues)

Table 2 (continued). Chemotherapy-induced anemia: lung cancer*

Treatment	Study/type (reference no.)	Regimen	No. of evaluable patients	Anemia,† % of patients	
				Grade 1 or 2	Grade 3 or 4
		Etop: 37.5 mg/m^2 PO daily on d 1–14 Ifo: 1.2 g/m^2 IV on d 1–4§§ Cis: 20 mg/m^2 IV on d 1–4 Cycles repeated every 28 d	20	NR	40‡‡
Carboplatin–paclitaxel–etoposide (CPE)	Hainsworth et al., 1997/phase II‖‖ *(75)*	Carbo: AUC 5 1-h IV Pac: 135 mg/m^2 1-h IV Etop: 50/100 mg PO on d 1–10 Cycles repeated every 21 d##	38	NR	32#
		Carbo: AUC 6 1-h IV Pac: 200 mg/m^2 1-h IV Cycles repeated every 21 d Etop: 50/100 mg PO on d 1–10 Cycles repeated every 21 d##	79	NR	35#

*IV = intravenous; PO = oral; Pac = paclitaxel; Carbo = carboplatin; G-CSF = granulocyte colony-stimulating factor; Cis = cisplatin; Etop = etoposide; Gem = gemcitabine; Vino - vinorelbine; Mit = mitomycin C; Vin = vinblastine; Ifo = ifosfamide; AUC = carboplatin dosed by the Calvert formula to an area under the concentration-versus-time curve; Cyclo = cyclophosphamide; Dox = doxorubicin; Vinc = vincristine; NR = not reported.

†National Cancer Institute Common Toxicity Criteria, unless otherwise specified.

‡Toxicity was graded according to the World Health Organization toxicity grading system.

§Initial vinorelbine dose.

‖Toxicity reported as percent of courses.

¶Mitomycin C was given on alternate cycles.

#Toxicity was graded according to Eastern Cooperative Oncology Group criteria.

**Toxicity was graded according to the Cancer and Leukemia Group B Expanded Common Toxicity Criteria.

††Mesna was delivered at a dose of 300 mg/m^2 by IV bolus before the first dose of ifosfamide and then as a continuous infusion at a dose of 1200 mg/m^2 on days 1–4.

‡‡Toxicity grading system was not specified.

§§Mesna was delivered at a dose of 120 mg/m^2 by IV bolus before ifosfamide on day 1 for each course and then as a continuous infusion at 400 mg/m^2 every 8 hours for 4 days.

‖‖Included patients with limited-stage disease.

##Etoposide at 50 mg alternating with 100 mg.

been observed with gemcitabine in patients with advanced NSCLC *(43–45)*.

Small-Cell Lung Cancer

Combination chemotherapy produces higher response rates and higher percentages of long-term survivors in patients with advanced small-cell lung cancer (SCLC) than traditional single-agent chemotherapy and is considered to be first-line treatment for this tumor *(27,60)*. The combination of cisplatin and etoposide is one of the most widely used regimens. Grade 3 or 4 anemia is commonly associated with this regimen, occurring in 16%–55% of the patients (Table 2, B); several phase II and III trials did not report the incidence of lesser grades of anemia *(67–69)*. Carboplatin plus etoposide is at least as active in patients with advanced SCLC as cisplatin plus etoposide but produces less nonhematologic toxicity *(22)*. In previously untreated patients with advanced disease, carboplatin–etoposide produced grade 1 or 2 anemia in 39% of the patients, whereas the incidence was 59% with cisplatin–etoposide *(70)*. The incidence of grade 3 or 4 anemia produced by carboplatin–etoposide (54%) in previously untreated patients with extensive-stage SCLC has been reported to be as high as that observed with cisplatin–etoposide *(71)*.

Combination cyclophosphamide–doxorubicin–vincristine (CAV) chemotherapy was one of the first standard regimens for SCLC and remains one of the most commonly used *(22)*. Anemia of grades 1–4 was observed in 13% and 54% of the patients with SCLC with low and high doses of the CAV combination, respectively (Table 2, B) *(72)*. A number of investigators have evaluated combinations of etoposide–ifosfamide–cisplatin (VIP) and ifosfamide–carboplatin–etoposide (ICE) in previously untreated patients with extensive-stage SCLC. Although the incidence of grade 3 or 4 anemia observed in the patients receiving VIP ranged from 31% to 53% *(68,74)*, anemia of this degree occurred in only 6%–11% of the patients receiving ICE *(73)*. However, more than 75% of the patients treated with two different dosing regimens of ICE experienced grade 1 or 2 anemia *(73)*. The combination of carboplatin–paclitaxel–oral etoposide produced a similar incidence of grade 3 or 4 anemia (32%–35%) as did the VIP combination in previously untreated patients with SCLC; lesser grades were not reported *(75)*.

Several new agents, including paclitaxel, docetaxel, vinorelbine, and topotecan, are currently being evaluated as single-agent therapies for the treatment of extensive-stage SCLC (Table 2, B). Docetaxel and topotecan produced grade 1 or 2 anemia in 60% of the patients and in 87% of the courses, respectively, in previously treated patients with extensive-stage SCLC; grade 3 or 4 anemia was observed in 3% of the patients and in 12% of the courses, respectively *(63,66)*. In previously untreated patients, topotecan produced grade 3 anemia in 15% of the patients *(62)*.

Breast Cancer

Conventional therapeutic regimens for the treatment of metastatic breast cancer include various combinations of doxorubicin, mitoxantrone, cyclophosphamide, methotrexate, and 5-flu-

Table 3. Chemotherapy-induced anemia: metastatic breast cancer*

Treatment	Study/type (reference No.)	Regimen	No. of evaluable patients	Anemia,† % of patients†	
				Grade 1 or 2	Grade 3 or 4
Single agent					
Previously untreated patients					
Paclitaxel	Davidson, 1996/phase II *(76)*	225 mg/m^2 3-h IV; cycles repeated every 21 d	30	93‡	7 (grade 3)‡
Docetaxel	Chevallier et al., 1995/phase II *(77)*	100 mg/m^2 1-h IV; cycles repeated every 21 d	34	97‡	0‡
	Hudis et al., 1996/phase II *(78)*	100 mg/m^2 1-h IV; cycles repeated every 21 d	37	NR	14 (grade 3)§
Vinorelbine	Weber et al., 1995/phase II *(79)*	30 mg/m^2 20-min IV; cycles repeated every 7 d	59	67‡	14‡
	Fumoleau et al., 1993/phase II *(80)*	30 mg/m^2 20-min IV; cycles repeated every 7 d	143	71‡	5‡
Previously treated patients					
Paclitaxel	Nabholtz et al., 1996/phase III *(81,98)*	135 mg/m^2 3-h IV	229	45‡	2‡
		175 mg/m^2 3-hr IV; cycles repeated every 21 d	229	51‡	4‡
	Dieras et al., 1995/phase II *(82)*	175 mg/m^2 3-h IV; cycles repeated every 21 d	38	36‡	27‡
	Seidman et al., 1995/phase II *(83)*	250 mg/m^2 24-h IV; G-CSF; 5 μg/kg SC on d 3–10; cycles repeated every 21 d	76	49§	30§
Docetaxel	Valero et al., 1995/phase II *(84)*	100 mg/m^2 1-h IV; cycles repeated every 21 d	35	60	11 (grade 3)
	Ravdin et al., 1995/phase II *(85)*	100 mg/m^2 1-h IV; cycles repeated every 21 d	41	85	10 (grade 3)
Vinorelbine	Gasparini et al., 1994/phase II *(86)*	20 mg/m^2 1-h IV; cycles repeated every 7 d	67	6‡	3‡
	Degardin et al., 1994/phase II *(87)*	30 mg/m^2 20-min IV; cycles repeated every 7 d	100	18‡	9 (grade 3)‡
	Jones et al., 1995/phase III *(88)*	30 mg/m^2 20-min IV; cycles repeated every 7 d	115	NR	14§
Combination therapy					
Previously untreated patients					
Cyclophosphamide–doxorubicin–5-fluorouracil–methotrexate (CAF-M)	Budd et al., 1995/phase III *(89)*	Cyclo: 500 mg/m^2 IV Dox: 50 mg/m^2 IV 5-FU: 500 mg/m^2 IV on d 1 and 8 Meth: 50 mg/m^2 IV on d 22 Cycles repeated every 21 d	266	27‖	1 (grade 3)‖
Cyclophosphamide–methotrexate–5-fluorouracil–vincristine (CMFV)	Budd et al., 1995/phase III *(89)*	Cyclo: 60 mg/m^2 PO d Meth: 15 mg/m^2 IV 5-FU: 400 mg/m^2 IV Vin: 0.625 mg/m^2 IV Cycles repeated every 7 d	264	25‖	2 (grade 3)‖
Cyclophosphamide–mitoxantrone–vincristine (CMV)	Bezwoda et al., 1995/phase III *(90)*	Cyclo: 600 mg/m^2 IV Mit: 12 mg/m^2 IV Vin: 1.4 mg/m^2 IV Cycles repeated every 42 d	45	NR	9¶
		Cyclo: 2.4 g/m^2 IV Mit: 35–45 mg/m^2 IV Vin: 2.5 g/m^2 IV Cycles repeated every 21 d	45	NR	80¶
Paclitaxel–doxorubicin	Gianni et al., 1995/phase I/II *(91)*	Pac: 125–175 mg/m^2 3-h IV** Dox: 60 mg/m^2 30-min IV Cycles repeated every 21 d	9	78‡	11‡
		Pac: 200 mg/m^2 3-h IV** Dox: 60 mg/m^2 30-min IV Cycles repeated every 21 d	25	84‡	8‡
Previously treated patients					
Cyclophosphamide–doxorubicin–5-fluorouracil (CAF)	Aisner et al., 1995/phase III *(92)*	Cyclo: 500 mg/m^2 IV Dox: 50 mg/m^2 IV 5-FU: 500 mg/m^2 IV on d 1 and 8 Cycles repeated every 21 d	165	55§	11§
Paclitaxel–doxorubicin	Gehl et al., 1996/phase I/II *(93)*	Pac: 175 mg/m^2 3-h IV Dox: 60 mg/m^2 30-min IV Cycles repeated every 21 d	21	59#	<1 (grade 3)#

*IV = intravenous; NR = not reported; G-CSF = granulocyte colony-stimulating factor; SC = subcutaneous; Cyclo = cyclophosphamide; Dox = doxorubicin; 5-FU = 5-fluorouracil; Pac = paclitaxel; Meth = methotrexate; PO = oral; Vin = vincristine; Mit = mitoxantrone.

†National Cancer Institute Common Toxicity Criteria, unless otherwise specified.

‡Toxicity was graded according to the World Health Organization toxicity grading system.

§Toxicity grading system not specified.

#Toxicity reported as % of courses.

‖Toxicity was graded according to Southwestern Oncology Group criteria.

¶Percent of patients who received blood transfusions.

**The starting dose of paclitaxel was 125 mg/m^2 and was increased by 25 mg/m^2 in subsequent cohorts of at least three patients until dose-limiting toxicity.

orouracil (5-FU) as well as mitomycin C with or without vinblastine *(22,23,25,26).* New active agents include paclitaxel, docetaxel, and vinorelbine *(25,26).* The reported incidence of grade 3 or 4 anemia associated with conventional combination chemotherapeutic regimens used in the treatment of breast cancer has ranged from less than 1% with the combination of 5-FU–doxorubicin–cyclophosphamide–methotrexate to 80% with high-dose cyclophosphamide–mitoxantrone–etoposide (Table 3)

Table 4. Chemotherapy-induced anemia: advanced ovarian cancer*

Treatment	Study/type (reference No.)	Regimen	No. of evaluable patients	Anemia,† % of patients	
				Grade 1 or 2	Grade 3 or 4
Single agent					
Previously untreated patients					
Carboplatin	Jones et al., 1992/phase II *(95)*	AUC 6 IV	36	NR	0‡
		AUC 12 IV	39	NR	26‡
		Cycles repeated every 28 d			
	Rozencweig et al., 1990/Meta-analysis *(96)*	400 mg/m^2 IV; cycles repeated every 28 d	87	66‡	7‡
Cisplatin	Rozencweig et al., 1990/Meta-analysis *(96)*	100 mg/m^2 IV; cycles repeated every 28 d	171	8‡	2‡
Previously treated patients					
Paclitaxel	Eisenhauer et al., 1994 *(97,98)*	135 mg/m^2 3-h IV	98	62‡	6‡
		175 mg/m^2 3-h IV	95	73‡	11‡
		135 mg/m^2 24-h IV	105	78‡	10‡
		175 mg/m^2 24-h IV	105	78‡	12‡
		Cycles repeated every 21 d			
	Thigpen et al., 1994/phase II *(99)*	170 mg/m^2 24-h IV; cycles repeated every 21 d§	45	18‖	7‖
	ten Bokkel Huinink et al., 1997/phase III (100)	175 mg/m^2 3-h IV; cycles repeated every 21 d	114	NR	6
	Einzig et al., 1992/phase II *(101)*	250 mg/m^2 24-h IV; cycles repeated every 21 d§	34	76¶	24¶
	Kohn et al., 1994/phase II *(102)*	250 mg/m^2 24-h IV; cycles repeated every 21 d; G-CSF: 10 μg/kg SC daily	47	36‡	64‡
Topotecan	ten Bokkel Huinink et al., 1997/phase III *(100)*	1.5 mg/m^2 30-min IV for 5 d; cycles repeated every 21 d	112	NR	40‖
	Creemers et al., 1996/phase II *(103)*	1.5 mg/m^2 30-min IV for 5 d; cycles repeated every 21 d§	111	67	32
	Kudelka et al., 1996/phase II *(104)*	1.5 mg/m^2 30-min IV for 5 d; cycles repeated every 21 d§	28	64**	31 (grade 3)**
Docetaxel	Francis et al., 1994/phase II *(105)*	100 mg/m^2 1-hr IV; cycles repeated every 21 d§	25	58	42 (grade 3)
	Kavanagh et al., 1996/phase II *(106)*	100 mg/m^2 1-hr IV; cycles repeated every 21 d§	55	60‡	27‡
	Piccart et al., 1995/phase II *(107)*	100 mg/m^2 1-hr IV; cycles repeated every 21 d§	90	87††	
Etoposide	Hoskins and Swenerton, 1994/phase II *(108)*	100 mg PO on d 1–14; cycles repeated every 21 d	27	56¶	7 (grade 3)¶
	Rose et al., 1998/phase II *(109)*	50 mg/m^2 PO on d 1–21; cycles repeated every 28 d§	97	31‡	13‡
Ifosfamide	Dorval et al., 1996/phase II *(110)*	1.5 mg/m^2 IV on d 1–5; cycles repeated every 28 d‡‡	41	NR	5**
	Sutton et al., 1989/phase II *(111)*	1.0 g/m^2 24-hr IV on d 1–7; cycles repeated every 28 d§§	19	NR	32 (grade 3)‡
Combination therapy					
Previously untreated patients					
Paclitaxel–cisplatin	McGuire et al., 1996/phase III *(112)*	Pac: 135 mg/m^2 24-h IV Cis: 75 mg/m^2 IV Cycles repeated every 21 d	182	58‖	8‖
Paclitaxel–carboplatin	Skarlos et al., 1997/phase II *(113)*	Pac: 175 mg/m^2 3-h IV Carbo: AUC 7 1-h IV Cycles repeated every 28 d	49	51‡	2 (grade 3)‡
Paclitaxel–cisplatin–cyclophosphamide	Coeffic et al., 1997/phase I/II *(114)*	Pac: 175 mg/m^2 3-h IV Cis: 80 mg/m^2 IV Cyclo: 600 mg/m^2 IV Cycles repeated every 21 d	23	17‡	5 (grade 3)‡
Carboplatin–cyclophosphamide	Alberts et al., 1992/phase III *(115)*	Carbo: 300 mg/m^2 IV‖‖ Cyclo: 600 mg/m^2 IV Cycles repeated every 28 d‖‖	148	98¶¶	3 (grade 3)¶¶
	Swenerton et al., 1992/phase III *(116)*	Carbo: 300 mg/m^2 1-h IV Cyclo: 600 mg/m^2 IV Cycles repeated every 28 d	207	41¶	42 (grade 3)¶
Cisplatin–cyclophosphamide	McGuire et al., 1996/phase III *(112)*	Cis: 50 mg/m^2 IV Cyclo: 500 mg/m^2 IV Cycles repeated every 21 d	235	32**	2 (grade 3)**

(Table continues)

Table 4 (continued). Chemotherapy-induced anemia: advanced ovarian cancer*

Treatment	Study/type (reference No.)	Regimen	No. of evaluable patients	Anemia,† % of patients	
				Grade 1 or 2	Grade 3 or 4
	Swenerton et al., 1992/phase III *(116)*	Cis: 75 mg/m^2 3-h IV Cyclo: 600 mg/m^2 IV Cycles repeated every 28 d	10	53¶	29 (grade 3)¶
	McGuire et al., 1995/phase III *(117)*	Cis: 75 mg/m^2 IV every 21 d Cyclo: 750 mg/m^2 IV Cycles repeated every 21 d	200	53‖	8‖
	Alberts et al., 1992/phase III *(115)*	Cis: 100 mg/m^2 IV every 21 d Cyclo: 1000 mg/m^2 IV Cycles repeated every 21 d	223	43‡	9 (grade 3)‡
	Alberts et al., 1996/phase III *(118)*	Cis: 100 mg/m^2 IV Cyclo: 600 mg/m^2 IV Cycles repeated every 28 d	140	97¶¶	3 (grade 3)¶¶
		Cis: 100 mg/m^2 2-h IV Cyclo: 600 mg/m^2 IV Cycles repeated every 21 d	276	NR	25**
Cyclophosphamide–cisplatin–doxorubicin (CAP)	Conte et al., 1996/phase III *(119)*	Cyclo: 600 mg/m^2 IV Cis: 50 mg/m^2 30-min IV Dox: 45 mg/m^2 IV Cycles repeated every 28 d	62	6 (grades 1–3)‡	NR

*AUC = carboplatin dose by the Calvert formula to an area under the concentration-versus-time curve; IV = intravenous; NR = not reported; G-CSF = granulocyte colony-stimulating factor; SC = subcutaneous; PO = oral; Pac = paclitaxel; Cis = cisplatin; Carbo = carboplatin; Cyclo = cyclophosphamide; Dox = doxorubicin.

†National Cancer Institute Common Toxicity Criteria, unless otherwise specified.

‡Toxicity was graded according to the World Health Organization toxicity grading system.

§Treatment was continued until disease progression or unacceptable toxicity.

‖Toxicity was graded according to Gynecologic Oncology Group criteria.

¶Toxicity was graded according to Eastern Cooperative Oncology Group criteria.

#G-CSF was administered until the absolute granulocyte count was >1500/μL for 2 consecutive days or the total white blood cell count was >3000/μL.

**Toxicity grading system was not specified.

††Grade of anemia unspecified.

‡‡Dose was reduced to 1.2 g/m^2 due to toxicity and mesna at 0.3 g/m^2 was administered IV at 4, 8, and 12 h following ifosfamide infusion.

§§Mesna at 0.6 g/m^2 was administered in a 24-hour infusion for 7 days.

‖‖Infusion duration not reported.

¶¶Toxicity was graded according to Southwestern Oncology Group criteria.

(89,90). The commonly used combination of cyclophosphamide–doxorubicin–5-FU produced grade 1 or 2 anemia in 55% and grade 3 or 4 anemia in 11% of previously treated patients with metastatic breast cancer *(92)*.

Several new agents demonstrate high response rates in metastatic breast cancer, including paclitaxel, docetaxel, and vinorelbine (Table 3) *(25,26)*. These agents also produce a high incidence of grade 1 or 2 anemia. Paclitaxel produced grade 1 or 2 anemia in 36%–51% of previously treated patients with metastatic breast cancer *(81–83)*. With docetaxel, high incidences of grade 1 or 2 anemia have been observed (60%–97%) in both previously treated and previously untreated patients with metastatic breast cancer *(77,84,85)*. Grade 3 or 4 anemia was observed in 30% of the patients with anthracycline-resistant disease receiving a high paclitaxel dose (250 mg/m^2) administered over 24 hours compared with 2% of the patients with a lower dose (135 mg/m^2) administered over 3 hours *(81,83)*. Docetaxel produced grade 3 or 4 anemia in approximately 10% of the previously treated patients with metastatic disease *(84,85)* and approximately 7% of the previously untreated patients *(77,78)*.

Compared with the taxanes, vinorelbine is associated with a low incidence of grade 1 or 2 anemia (6%–18%) in previously treated patients with metastatic breast cancer *(86,87)*. In previously untreated patients with metastatic disease, vinorelbine produced higher incidences of grade 1 or 2 anemia (range, 67%–71%) *(79,80)*. Grade 3 or 4 anemia has been observed in 3%–14% of the patients with metastatic breast cancer, regardless of previous exposure to chemotherapy *(79,80,86–88)*.

Given their high activity, these newer agents are under extensive investigation in combination therapy. Combination paclitaxel–doxorubicin appears to be one of the most active chemotherapeutic regimens for the treatment of metastatic breast cancer. In previously untreated patients with metastatic breast disease, paclitaxel plus doxorubicin produced an overall response rate of 94%, including a complete response rate of 41% *(91)*. This regimen produced a high incidence of grade 1 or 2 anemia (78%–84%); the incidence of grade 3 or 4 anemia ranged from 8% to 11% *(91)*. In previously treated patients with metastatic breast cancer, paclitaxel–doxorubicin produced a lower incidence of both grade 1 or 2 anemia (59%) and grade 3 or 4 anemia (<1%) *(93)*.

Ovarian Cancer

In advanced ovarian cancer, platinum-based combination regimens are preferred for initial chemotherapy, and single agents are generally used in patients with recurrent disease *(23,31,94)*. Both paclitaxel and topotecan have been approved for the treatment of advanced ovarian cancer, and paclitaxel in combination with a platinum compound is considered the standard of care as first-line chemotherapy in the management of

Table 5. Chemotherapy-induced anemia: lymphomas*

Treatment	Study/type (reference No.)	Regimen	No. of evaluable patients	Anemia,† % of patients	
				Grade 1 or 2	Grade 3 or 4
Non-Hodgkin's lymphoma					
Procarbazine–methotrexate–leucovorin–doxorubicin–cyclophosphamide–etoposide (ProMACE) + MOPP	Sertoli et al., 1994/phase III *(120)*	Proc: 100 mg/m^2 PO on d 1–7 Meth: 1500 mg/m^2 IV on d 15 Leu: 50 mg/m^2 IV on d 15 Dox: 25 mg/m^2 IV on d 1 and 8 Cyclo: 650 mg/m^2 IV on d 1 and 8 Etop: 120 mg/m^2 IV on d 1 and 8 Cycles repeated every 28 d	114	63‡	9‡
Methotrexate–leucovorin–doxorubicin–cyclophosphamide–vincristine–prednisone–bleomycin (MACOP-B)	Sertoli et al., 1994/phase III *(120)*	Meth: 400 mg/m^2 IV, wk 2, 6, and 10 Leu: 15 mg PO, weeks 2, 6, and 10 Dox: 50 mg/m^2 IV, weeks 1, 3, 5, 7, 9, and 11 Cyclo: 350 mg/m^2 IV, weeks 1, 3, 5, 7, 9, and 11 Vin: 1.4 mg/m^2 IV, weeks 2, 4, 6, 8, 10, and 12 Pred: 75 mg PO d Bleo: 10 mg/m^2 IV, weeks 4, 8, and 12 Cycles repeated every 28 d	107	55‡	10‡
Cyclophosphamide–doxorubicin–vincristine–prednisone (CHOP)	Meyer et al., 1995/phase II *(121)*	Cyclo: 750 mg/m^2 IV Dox: 50 mg/m^2 IV Vin: 2 mg IV Pred: 75 mg PO on d 1–5 Cycles repeated every 21 days	19	NR	74 (grade 3)§
	Meyer et al. 1995/phase II *(121)*	Cyclo: 250 mg/m^2 IV on d 1, 8, and 15 Dox: 16.7 mg/m^2 IV on d 1, 8, and 15 Vin: 0.67 mg IV on d 1, 8, and 15 Pred: 75 mg PO on d 1–5 Cycles repeated every 21 d	19	NR	79 (grade 3)§
	Gordon et al., 1992/phase III *(122)*	Cyclo: 750 mg/m^2 IV Dox: 50 mg/m^2 IV Vin: 1.4 mg IV Pred: 100 mg/m^2 PO on d 1–5 Cycles repeated every 21 d	174	49‖	17 (grade 3)‖
Hodgkin's disease					
Mechlorethamine–vincristine–procarbazine–prednisone (MOPP)	Canellos et al., 1992/phase III *(123)*	Mec: 6 mg/m^2 IV on d 1 and 8 Vin: 1.4 mg/m^2 IV on d 1 and 8 Proc: 100 mg/m^2 PO on d 1–14 Pred: 40 mg/m^2 PO on d 1–14 Cycles repeated every 28 d	123	31¶	12#
Etoposide–vinblastine–doxorubicin	Canellos et al., 1995/phase II *(124)*	Etop: 100 mg/m^2 IV on d 1, 2, and 3 Vinb: 6 mg/m^2 IV Dox: 50 mg/m^2 IV Cycles repeated every 28 d	45	59 (grade 2)‡	13‡
Doxorubicin–bleomycin–vinblastine–dacarbazine (ABVD)	Canellos et al. 1992/phase III *(123)*	Dox: 25 mg/m^2 IV on d 1 and 15 Bleo: 10 U/d IV on d 1 and 15 Vinb: 6 mg/m^2 IV on d 1 and 15 Dac: 375 mg/m^2 IV on d 1 and 15	115	5¶	0#

*Proc = procarbazine; PO = oral; Meth = methotrexate; IV = intravenous; Leu = leucovorin; Dox = doxorubicin; Cyclo = cyclophosphamide; Etop = etoposide; Vin = vincristine; Pred = prednisone; Bleo = bleomycin; NR = not reported; Mec = mechlorethamine; Vinb = vinblastine; Dac = decarbazine.

†National Cancer Institute Common Toxicity Criteria, unless otherwise specified.

‡Toxicity grading system was not specified.

§Toxicity was graded according to Eastern Cooperative Oncology Group criteria.

‖Toxicity was graded according to the World Health Organization toxicity grading system.

¶Anemia classified as severe.

#Anemia classified as life threatening or fatal.

advanced disease *(31,94)*. In general, higher doses and longer infusion durations of paclitaxel are associated with increased myelosuppression, including an increased incidence of grade 3 or 4 anemia (Table 4) *(97,98)*. In patients with ovarian cancer who failed first-line therapy with a platinum-based chemotherapy regimen, paclitaxel doses of 135–175 mg/m^2 administered over 3 hours were associated with grade 1 or 2 anemia in 62%–73% of the patients *(97)*.

Topotecan is associated with a high incidence of grade 1 or 2 anemia and a higher incidence of grade 3 or 4 anemia than paclitaxel in previously treated patients (Table 4) *(100,103,104)*. In a phase III trial comparing topotecan and paclitaxel in patients with recurrent advanced disease, topotecan at a dose of 1.5 mg/m^2 was associated with a higher incidence of grade 3 or 4 anemia than paclitaxel at a dose of 175 mg/m^2 (3-hour infusion) (40% versus 6%); grade 4 anemia occurred in 4% and 3% of patients, respectively *(100)*. A high incidence of grade 3 or 4 anemia has been observed with docetaxel in patients with ovar-

Table 6. Chemotherapy-induced anemia: advanced colorectal cancer*

Treatment	Study/type (reference No.)	Regimen	No. of evaluable patients	Anemia,† % of patients	
				Grade 1 or 2	Grade 3 or 4
Single agent					
Previously untreated patients					
5-FU	Hill et al., 1995/phase III *(125)*	300 mg/m^2 per d 24-h IV for 70 d	78	54‡	8‡
	Petrelli et al., 1989/phase III *(126)*	500 mg/m^2 per d by IV bolus on d 1–5; cycles repeated every 28 d	107	50§	5‖
	Greco et al., 1996/phase III *(127)*	750 mg/m^2 per d 24-h IV on d 1–5 followed by 750 mg/m^2 by IV bolus every 7 d	123	50‡	5‡
Irinotecan	Rougier et al., 1997/phase II *(128)*	350 mg/m^2 30-min IV; cycles repeated every 21 d	48	60	8
Topotecan	Creemers et al., 1996/phase II *(129)*	0.5–0.6 mg/m^2 per d 24-h IV on d 1–21; cycles repeated every 28 d	41	58–90¶	
Previously treated patients					
Irinotecan	Rothenberg et al., 1996/phase II *(130)*	125–150 mg/m^2 IV every 7 d for 4 wk; cycles repeated every 56 d	48	NR	10‡
	Rougier et al., 1997/phase II *(128)*	350 mg/m^2 30-min IV; cycles repeated every 21 d	165	49	10
Combination therapy					
Previously untreated patients					
5-FU–leucovorin	Petrelli et al., 1989 *(126)*	5-FU: 600 mg/m^2 by IV bolus Leu: 25 mg/m^2 2-h IV Cycles repeated every 7 d	112	27§	3‖
		5-FU: 600 mg/m^2 by IV bolus Leu: 500 mg/m^2 2-h IV Cycles repeated every 7 d	109	46§	2‖
	Corfu-A Study Group, 1995/phase III *(131)*	5-FU: 370 mg/m^2 by IV bolus on d 1–5 Leu: 200 mg/m^2 IV on d 1–5 Cycles repeated every 28 d	242	53¶	5¶
	Kosmidis et al., 1996/phase III *(132)*	5-FU: 450 mg/m^2 by IV bolus Leu: 200 mg/m^2 2-h IV Cycles repeated every 7 d	53	6‡	2 (grade 3)‡
UFT–leucovorin	González-Barón et al., 1997/phase II *(133)*	UFT: 195 mg/m^2 PO d 1 Leu: 500 mg/m^2 IV d 1 UFT: 195 mg every 12 h PO on d 2–14 Leu: 15 mg every 12 h PO on d 2–14	75	3‡	0‡
	Sanchiz and Milla, 1994/phase II *(134)*	UFT: 600 mg/m^2 PO on d 1–14 Leu: 90 mg/m^2 PO on d 1–14	52	21 (grade 1)‡	0‡

*IV = intravenous; 5-FU = 5-fluorouracil; Leu = leucovorin; UFT = tegafur–uracil; PO = orally.
†National Cancer Institute Common Toxicity Criteria, unless otherwise specified.
‡Toxicity was graded according to the World Health Organization toxicity grading system.
§Mild to moderate anemia.
‖Severe or worse anemia.
¶Percent of patients requiring transfusion in treatment cycles 1–6.

ian cancer who were previously treated with platinum-containing chemotherapy *(105,106)*. In a phase II trial by Piccart et al. *(107)*, the overall incidence of anemia in patients treated with docetaxel alone was 87%, although the incidence of anemia by grade was not reported. Incidences of grade 1 or 2 anemia are high and range from 18% to 76% with single-agent docetaxel, paclitaxel, and topotecan in patients with advanced ovarian cancer previously treated with platinum-containing chemotherapy *(97–99,101–109)*.

Single-agent carboplatin and cisplatin in previously untreated patients are associated with relatively low incidences (0%–7%) of grade 3 or 4 anemia *(95,96)*. Several phase III trials of combination chemotherapy have been conducted in previously untreated patients with advanced ovarian cancer, and platinum-based combinations consistently produced high incidences of grade 1 or 2 anemia (Table 4). Carboplatin or cisplatin in combination with cyclophosphamide produced similar incidences of grade 1 or 2 anemia (98% and 97%, respectively) *(115)*. The incidences of grade 3 or 4 anemia in phase III trials of combination chemotherapy ranged from 2% to 42% with cyclophosphamide–platinum *(112,115–118)* and from 2% to 8% with paclitaxel–platinum *(112)*. In patients with advanced disease in phase III trials performed by the Southwest Oncology Group *(115,118)*, platinum-based chemotherapy was associated with a 33% RBC transfusion rate *(19)*. In a logistic regression analysis, baseline hemoglobin, age, and platinum analogue (cisplatin was more likely than carboplatin to induce anemia) were statistically significant ($P \leq .001$) predictors of the need for RBC transfusion.

Lymphomas

Therapeutic regimens proven to be effective for the treatment of advanced Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL; specifically, large-cell follicular lymphoma and diffuse large-B-cell lymphoma) include various combinations of

Table 7. Chemotherapy-induced anemia: advanced head and neck cancer*

Treatment	Study/type (reference No.)	Regimen	No. of evaluable patients	Anemia,† % of patients	
				Grade 1 or 2	Grade 3 or 4
Single agent					
Previously untreated patients					
Paclitaxel	Forastiere et al., 1993/phase II *(136)*	250 mg/m^2 24-h IV; G-CSF: 5 μg/kg SC on d 3–15; cycles repeated every 21 d	23	39 (grade 2)‡	13 (grade 3)‡
Docetaxel	Catimel et al., 1994/phase II *(137)*	100 mg/m^2 1-h IV; cycles repeated every 21 d	39	74	5
Topotecan	Smith et al., 1996/phase II¶ *(138)*	1.5 mg/m^2 d 1–5; cycles repeated every 21 d	29	31 (grade 2)‖	4‖
5-FU	Jacobs et al., 1992/phase III *(139)*	1000 mg/m^2 24-h IV d 1–4; cycles repeated every 21 d	82	NR	11‖
Cisplatin	Jacobs et al., 1992/phase III *(139)*	100 mg/m^2 20-min IV; cycles repeated every 21 d	83	NR	11‖
Methotrexate	Forastiere et al. 1992/phase III¶ *(140)*	40 mg/m^2 IV every 7 d	87	25‖	3 (grade 3)‖
Combination therapy					
Previously untreated patients					
5-FU–cisplatin	Jacobs et al., 1992/phase III *(139)*	5-FU: 1000 mg/m^2 24-h IV on d 1–4 Cis: 100 mg/m^2 20-min IV Cycles repeated every 21 d	78	NR	12‖
	Forastiere et al., 1992/phase III¶ *(140)*	5-FU: 1000 mg/m^2 24-h IV d 1–4 Cis: 100 mg/m^2 IV Cycles repeated every 21 d	85	55‖	5‖
	Paredes et al., 1988/phase III¶ *(141)*	5-FU: 1000 mg/m^2 24-h IV on d 1–5 Cis: 120 mg/m^2 1-h IV Cycles repeated every 21 d	31	74‖	NR
5-FU–carboplatin	Forastiere et al., 1992/phase III¶ *(140)*	5-FU: 1000 mg/m^2 24-h IV on d 1–4 Carbo: 300 mg/m^2 IV Cycles repeated every 28 d	86	42‖	14‖
Paclitaxel–5-FU–cisplatin	Hussain et al., 1997/phase I/II *(142)*	Pac: 135–200 mg/m^2 3-h IV on d 1 5-FU: 1000 mg/m^2 IV on d 2–6 Cis: 75–100 mg/m^2 IV d 2 Cycles repeated every 21 d	17	35‖	12 (grade 3)‖
Paclitaxel–ifosfamide–cisplatin	Shin et al., 1998/phase II *(143)*	Pac: 175 mg/m^2 3-h IV Ifos: 1000 mg/m^2 2-h IV on d 1–3 Cis: 60 mg/m^2 IV Cycles repeated every 21–28 d	52	NR	12#
Paclitaxel–carboplatin	Fountzilas et al., 1997/phase II *(144)*	Pac: 200 mg/m^2 3-h IV Cis: AUC 7 30-min IV G-CSF: 5 μg/kg SC on d 2–12 Cycles repeated every 28 d	49	24‖	2 (grade 4)‖

*IV = intravenous; 5-FU = 5-fluorouracil; Cis = cisplatin; Carbo = carboplatin; Pac = paclitaxel; Ifos = ifosfamide; AUC = carboplatin dosed by the Calvert formula to an area under the concentration-versus-time curve; G-CSF = granulocyte colony-stimulating factor; SC = subcutaneous.

†National Cancer Institute Common Toxicity Criteria, unless otherwise specified.

‡Toxicity grading system was unspecified.

§G-CSF was administered until the absolute granulocyte count was >1500/μL.

‖Toxicity was graded according to the World Health Organization toxicity grading system.

¶The majority of patients received no prior chemotherapy.

#Percent of patients requiring blood transfusions.

methotrexate with leucovorin, doxorubicin, cyclophosphamide, vincristine, dexamethasone or prednisone, vinblastine, etoposide, and bleomycin *(21–23,32)*. Many of the standard combinations used in treating advanced HD and NHL are associated with anemia (Table 5). Treatment with the combinations of procarbazine–methotrexate–leucovorin–doxorubicin–cyclophosphamide–etoposide, mechlorethamine–vincristine–procarbazine–prednisone (MOPP), and methotrexate–leucovorin–doxorubicin–cyclophosphamide–vincristine–prednisone–bleomycin produced grade 1 or 2 anemia in 63% and 55% and grade 3 or 4 anemia in 9% and 10% of the patients with NHL, respectively *(120)*. Another combination chemotherapy for NHL (cyclophosphamide–doxorubicin–vincristine–prednisone) produced grade 3 anemia in 74% of the NHL patients by use of a standard dosing schedule and 79% of the patients with the use of a weekly schedule *(121)*.

MOPP combination therapy is considered first-line treatment in older patients with advanced HD and in patients for whom anthracycline-containing regimens are contraindicated. In a phase III study comparing MOPP with combination doxorubicin–bleomycin–vinblastine–dacarbazine (ABVD), MOPP produced a higher incidence of both grade 1 or 2 and grade 3 or 4 anemia (Table 5) *(123)*. Grade 1 or 2 and grade 3 or 4 anemia was observed in 31% and 12% of patients who received MOPP, respectively, and in 5% and 0% of the patients who received ABVD, respectively *(123)*. Attempts to improve salvage therapy

Table 8. Risks of blood transfusion *(146)**

Risk factor	Estimated frequency		No. of deaths per million units	Reference Nos.
	Per million units	Per actual unit		
Infection				
Viral				
Hepatitis A	1	1/1 000 000	0	*(147)*
Hepatitis B	7–32	1/30 000–1/250 000	0–0.14	*(148)*
Hepatitis C	4–36	1/30 000–1/150 000	0.5–17	*(148)*
HIV	0.4–5	1/200 000–1/2 000 000	0.5–5	*(148,149)*
HTLV types I and II	0.5–4	1/250 000–1/2 000 000	0	*(148)*
Parvovirus B19	100	1/10 000	0	*(147)*
Bacterial				
Red blood cells	2	1/500 000	0.1–0.25	*(147,150)*
Platelets	83	1/12 000	21	*(147)*
Acute hemolytic reactions	1–4	1/250 000–1/1 000 000	0.67	*(150,151)*
Delayed hemolytic reactions	1000	1/1000	0.4	*(150–153)*
Transfusion-related acute lung injury	200	1/5000	0.2	*(151,154)*

*HIV = human immunodeficiency virus; HTLV = human T-cell lymphotropic virus. Reproduced with permission from Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine: blood transfusion. N Engl J Med 1999;340:438–47. Copyright © 1999 Massachusetts Medical Society. All rights reserved.

in patients with relapsed or refractory HD with etoposide–vinblastine–doxorubicin resulted in "severe" anemia in 13% of the patients and "moderate or serious" anemia in 59% *(124)*.

Colorectal Cancer

5-FU has been the mainstay of chemotherapy for advanced colorectal cancer for the past 40 years, and it is frequently used in combination with leucovorin or levamisole *(23,28)*. Single-agent 5-FU administered by continuous or bolus IV infusion produces grade 1 or 2 anemia in approximately 50% and grade 3 or 4 anemia in 5%–8% of previously untreated patients with advanced disease (Table 6) *(125–127)*. Modulation of 5-FU and UFT (tegafur and uracil), a 5-FU prodrug, has been shown to be effective for the treatment of advanced colorectal cancer. Overall, therapy with bolus 5-FU plus leucovorin *(126,131,132)* or UFT–leucovorin produces little to no grade 3 or 4 anemia (0%–5%) *(133,134)*. However, bolus 5-FU plus leucovorin produced frequent grade 1 or 2 anemia (27%–53%) *(126,131)*.

Irinotecan, a camptothecin, was recently introduced for the treatment of advanced colorectal cancer. Irinotecan is associated with a high incidence of grade 1 or 2 anemia (49%–60%) *(128)*; grade 3 or 4 anemia occurs in 8%–10% of the patients *(128,130)*. Topotecan, another camptothecin, has also been investigated in the treatment of advanced colorectal cancer. Blood transfusions were required in 58% of the patients during treatment cycle 1 and in 90% of the patients during treatment cycle 6 with single-agent therapy *(129)*.

Head and Neck Cancer

The most active single agents for head and neck cancer are methotrexate, bleomycin, cisplatin, carboplatin, 5-FU, and the new agents docetaxel, paclitaxel, and gemcitabine *(22,23,30,135)*. Overall, single-agent therapies for the treatment of advanced-stage disease are associated with high incidences of grade 1 or 2 anemia and low incidences of grade 3 or 4 anemia (Table 7). Single-agent paclitaxel and single-agent methotrexate produced grade 1 or 2 anemia in 39% and 25% and grade 3 anemia in 13% and 3% of the previously untreated patients with advanced head and neck cancer, respectively *(136,140)*. Docetaxel produced grade 1 or 2 anemia in 74% and grade 3 or 4 anemia in 5% of the patients with advanced disease *(137)*.

Numerous trials of platinum-based combination chemotherapy have been conducted in patients with head and neck cancer in an effort to improve response rates and survival. Although carboplatin is generally less toxic than cisplatin, combination chemotherapy with 5-FU–cisplatin, 5-FU–carboplatin, paclitaxel–cisplatin, and paclitaxel–carboplatin produced similar incidences of grade 1 or 2 and grade 3 or 4 anemia (Table 7) *(139–141,144)*. 5-FU–cisplatin produced grade 1 or 2 anemia in 55%–74% *(140,141)* and grade 3 or 4 anemia in 5%–12% *(139,140)* of the patients. Paclitaxel–5-FU–cisplatin produced grade 1 or 2 anemia in 35% and grade 3 anemia in 12% of the patients *(142)*. Blood transfusions were required in 12% of patients with advanced head and neck tumors treated with paclitaxel–ifosfamide–cisplatin *(143)*.

Management of Chemotherapy-Induced Anemia

Because anemia in cancer patients can result from many factors, treatment must be individualized and accompanied by correction or management of simple nutritional deficiencies, underlying infectious or inflammatory processes, hemolytic diseases, occult blood loss, or hemolysis. The management of anemia resulting from myelosuppressive chemotherapy depends on its severity. Treatment options include crystalloid and hematinic treatment, RBC transfusion, epoetin alfa administration, or a combination of options.

RBC Transfusions

Patients with symptomatic, but transient, anemia resulting from acute blood loss or those with symptomatic chronic anemia should receive crystalloids to replace intravascular volume *(145)*. If symptoms persist despite replacement therapy, patients should receive an RBC transfusion. Patients with normovolemic, but symptomatic, anemia should be assessed for iron, folate, or vitamin B_{12} deficiency and should receive appropriate replacement therapy to correct the deficiency. RBC transfusions are indicated in cancer patients with acute anemia following acute blood loss when crystalloid infusions do not adequately correct

intravascular volume, in those with chronic symptomatic anemia unresponsive to iron replacement, and in those in whom medical necessity does not allow adequate time for epoetin alfa to be effective *(145)*. RBC transfusions, while ameliorating anemia, are associated with risks, the most serious of which is the potential transmission of infectious diseases (Table 8). Although the blood supply is now carefully screened and the risk of HIV transmission is negligible, infectious agents, such as the hepatitis viruses, cytomegalovirus, Epstein-Barr virus, and exotic microbes, remain a concern. Other serious adverse events associated with allogeneic transfusion include alloimmunization, allergic reactions, hemolytic reactions, iron and circulatory overload, and possible immunosuppression. Milder side effects, such as fever and urticaria, are frequent *(155)*. Concern over the safety of the blood supply led to a downturn in blood donation rates during the 1980s *(156);* although collections have increased in the 1990s, this increase has been offset by increased demand, continuing the strain on the blood supply. For these reasons, transfusion is generally reserved for an acute emergency (e.g., hypovolemia secondary to blood loss), severely anemic patients with serious symptoms (e.g., syncope, dyspnea, angina), or when other underlying disease puts patients at risk for an adverse cardiac event in the setting of mild-to-moderate anemia *(145)*.

Epoetin Alfa

Erythropoietin is a hematologic growth factor that regulates the proliferation, maturation, and differentiation of RBCs. Several large, prospective, placebo-controlled studies have demonstrated the value of epoetin alfa, the human recombinant form of erythropoetin, for the treatment of anemia in cancer patients. The largest study included 413 patients, 68% of whom had solid tumors *(157)*. Patients were grouped according to treatment regimen—no chemotherapy, myelosuppressive non-cisplatin-containing chemotherapy, and myelosuppressive cisplatin-containing chemotherapy—and randomly assigned to receive either placebo or epoetin alfa. Patients in the no-chemotherapy arm received epoetin alfa at a dose of 100 U/kg three times weekly for 8 weeks, and those in the two chemotherapy arms received epoetin alfa at a dose of 150 U/kg three times weekly for 12 weeks. In all three groups, patients receiving epoetin alfa had a statistically significant increase in hematocrit compared with placebo-treated patients ($P<.004$; all tests were two-sided). Transfusions were reduced in the two chemotherapy groups but not in the nonchemotherapy group; the lack of a reduction in the nonchemotherapy group may have been related to the lower dose and shorter treatment duration in this arm. Compared with patients who received placebo, those who received epoetin alfa and who had an increase in hematocrit of at least 6% also had statistically significant improvements in energy level, ability to perform daily activities, and overall QOL ($P<.05$). The double-blind phase of this trial was followed by an open-label phase in which 347 patients continued to receive epoetin alfa doses up to 300 U/kg three times weekly for up to 6 additional months. By the end of the treatment, an increase in hematocrit of at least 6% was observed in 40%, 56%, and 58% of no-chemotherapy, non-cisplatin-containing chemotherapy, and cisplatin-containing chemotherapy patients, respectively; requirements for transfusions decreased from 31%, 25%, and 43%, respectively, to 10%, 13%, and 12%, respectively.

In another study, 100 patients with cisplatin-induced anemia were randomly assigned to receive epoetin alfa or placebo. Statistically significant increases in mean hemoglobin levels occurred in the epoetin alfa group after the 3rd, 6th, and 9th weeks of therapy compared with baseline ($P\leqslant.01$, two-sided tests); increases were not observed in patients receiving placebo. In addition, 20% of the patients in the epoetin alfa arm required transfusions compared with 56% of the patients receiving placebo *(158)*.

The beneficial effects of epoetin alfa on anemia, functional status, and QOL are also supported by two large, nonrandomized, open-label, multicenter community studies *(7,8)*. In the first study, the impact of epoetin alfa therapy on hemoglobin, transfusion requirements, and QOL was evaluated in more than 2000 anemic cancer patients with various nonmyeloid malignancies receiving cytotoxic chemotherapy *(7)*. Patients were treated with epoetin alfa at a dose of 150 U/kg three times weekly for up to 4 months; the dose could have been doubled after 8 weeks if there was an inadequate therapeutic response. Of 2030 patients, 1047 completed all 4 months of epoetin alfa therapy. Patients who received epoetin alfa treatment had a 1.8-g of hemoglobin/dL increase from baseline to final hemoglobin level ($P<.001$; all tests were two-sided) and experienced progressive and statistically significant increases in hemoglobin levels at each monthly visit ($P<.001$). In addition, statistically significantly fewer patients who received epoetin alfa were transfused ($P<.001$), and fewer transfusions were administered per patient per month after the first month of treatment. Epoetin alfa treatment was associated with statistically significant increases in mean self-rated scores on the Linear Analog Scale Assessment (LASA) for energy level ($P<.001$), activity level ($P<.001$), and overall QOL ($P<.001$). A direct and statistically significant correlation was observed between the magnitude of the increase in hemoglobin level and the magnitude of improvement in each of the QOL parameters (energy: $r = .30$, $P<.001$; activity: $r = .28$, $P<.001$; overall QOL: $r = .27$, $P<.001$). In a retrospective analysis of a subgroup of patients for whom tumor response data were available, these improvements were also independent of tumor response and even occurred in a subgroup of patients with progressive disease whose hemoglobin levels increased by 4 g/dL, thus providing strong evidence that the increases in QOL were in part because of increases in hemoglobin *(7)*.

In a second trial, Demetri et al. *(8)* prospectively evaluated the potentially confounding effect of tumor response in 2289 patients with nonmyeloid malignancies receiving chemotherapy who received epoetin alfa at a dose of 10 000 U three times weekly, for a maximum of 16 weeks. Doubling of the dose could occur after 4 weeks if the hemoglobin increase was less than 1 g/dL. Statistically significant increases in the hemoglobin level ($P<.001$) and statistically significant decreases in the percentage of patients who required transfusions ($P<.001$) were observed for all tumor types. QOL was measured by use of two validated instruments, FACT-An and LASA. Epoetin alfa therapy was associated with statistically significant improvements in FACT-An and Anemia Subscale scores (both $P<.001$) and with statistically significant increases in QOL measures on the LASA—i.e., scores for energy level ($P<.001$), activity level ($P<.001$), and overall well-being ($P<.001$). Increases in QOL measures based on the LASA were observed as soon as 1 month after the start of therapy. The increase in overall QOL was statistically significantly correlated ($r = .235$, $P<.001$) with an increase in hemoglobin level and was independent of tumor response, indi-

cating that both hemoglobin level and disease response are independent variables that significantly impact QOL. Collectively, these results suggest that cancer patients undergoing chemotherapy can achieve important therapeutic benefit from treatment of anemia with epoetin alfa and that treating anemia may greatly improve patient functional ability and QOL.

Before epoetin alfa therapy is initiated in anemic cancer patients receiving chemotherapy, patients should be evaluated for causes of anemia. The initial dosage of epoetin alfa is 10 000 U subcutaneously three times weekly *(8)*. After 4 weeks of therapy, if the hemoglobin level is not increased by at least 1 g/dL, dosage should be increased to 20 000 U three times weekly. Patients who do not respond to the higher dosage are unlikely to respond with further dosage increases. Patients may require supplemental iron to avoid depletion of iron stores and to adequately support the erythropoiesis stimulated by epoetin alfa administration; iron stores should be monitored over time as appropriate.

Studies *(159,160)* have been performed to determine the potential role of epoetin alfa in preventing chemotherapy-induced anemia. Crawford et al. *(159)* compared the effect of epoetin alfa with placebo for the prevention of chemotherapy-related anemia in 27 patients with SCLC who received cyclophosphamide, doxorubicin, etoposide, and granulocyte colony-stimulating factor. In a previous clinical trial *(161)*, this chemotherapy regimen had produced anemia in 100% of the patients, with 80% requiring transfusions. Patients received either placebo (n = 13) or epoetin alfa (75 U/kg per day, subcutaneously; n = 14) beginning on day 1 and continuing through six chemotherapy cycles. The study drug was unblinded if patients developed anemia (hematocrit <32% on day 1 of any cycle after cycle 1) that required transfusion. Patients who received epoetin alfa completed a median of 3.7 cycles before requiring transfusion compared with a median of 1.5 cycles for those receiving placebo ($P = .01$). The median time to transfusion was 96 days and 43 days in patients receiving epoetin alfa and placebo, respectively. In a recent phase I trial in previously untreated patients with advanced head and neck carcinoma *(160)*, patients received up to three cycles of paclitaxel and carboplatin with (n = 14) or without (n = 22) epoetin alfa before radiation therapy or surgery. Patients treated with epoetin alfa experienced a mean hemoglobin decrease of 0.5 g/dL during preoperative chemotherapy versus a decrease of 3.3 g of hemoglobin/dL in patients who did not receive epoetin alfa ($P<.0001$). In addition, fewer patients treated with epoetin alfa received RBC transfusions during preoperative chemotherapy (0% versus 18%). The results of these trials suggest that epoetin alfa can prevent chemotherapy-induced anemia and can reduce the need for RBC transfusions when administered concomitantly with chemotherapy regimens that produce a high incidence of anemia.

Conclusions

The incidence of chronic anemia in adult cancer patients is determined by numerous factors, particularly the type, stage, and duration of malignancy and the type and intensity of previous and current treatment. Despite identified limitations in the grading and reporting of treatment-related anemia, which are evidenced in this review, the collective results confirm a relatively high incidence of mild-to-moderate anemia across the major nonmyeloid tumors treated with the most commonly used single agents and combination chemotherapy regimens. Platinum-based therapies, which are well recognized to cause anemia, continue to play a major role in the treatment of lung, ovarian, and head and neck malignancies. The highest incidence of anemia requiring transfusion occurs in patients with lymphomas, lung tumors, and gynecologic (e.g., ovarian) or genitourinary tumors, in whom the incidence may be as high as 50%–60%. The incidence of mild-to-moderate anemia is often even higher across many of the major solid tumors. The new generation of chemotherapeutic agents, particularly the antimicrotubular agents (taxanes, vinorelbine) and camptothecins, is myelosuppressive; many of these agents also exhibit radiosensitizing properties. These agents can be anticipated to play greater roles, especially in combination chemotherapy and combined modality regimens, in the treatment of major solid tumors. Thus, anemia will continue to affect large numbers of cancer patients, leading to a decrease in functional capacity and QOL, with the potential need for RBC transfusions and attendant risks and inconvenience.

Results of recent clinical trials suggest that mild-to-moderate anemia that is not routinely treated with, or persists after, RBC transfusions—and which frequently has been considered by clinicians to be clinically unimportant and asymptomatic—may be associated with decreased QOL. Advances in assessing the relationships between anemia, fatigue, and QOL in cancer patients are providing new insights, suggesting that the tradition of leaving lesser degrees of anemia untreated may compromise patients' functional ability and QOL. Consideration of treatment of mild-to-moderate anemia will likely become important as greater emphasis is placed on QOL in the management of the oncology patient. Future research on the relationships between hemoglobin levels, patient well-being, and symptoms may lead to new classifications of chemotherapy-induced anemia that would allow the more effective development of appropriate therapeutic interventions based on outcomes as well as hemoglobin levels. These new classifications may help to overcome the perception by oncologists and patients that lesser degrees of anemia must be endured without treatment.

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NOTES

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