Trends in Recommendations for Myelosuppressive Chemotherapy for the Treatment of Solid Tumors

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Key Words

Breast cancer, colorectal cancer, lung cancer, chemotherapy, myelosuppression, anemia, neutropenia, thrombocytopenia

Abstract

Lung, breast, and colorectal cancers are the 3 most frequent causes of cancer-related death in the United States. In the past 15 years, survival has increased dramatically for patients with these tumor types, partly because improved chemotherapy caused major changes in standard care. In addition, maintaining chemotherapy dose intensity has an established a positive effect on patient outcomes. However, delivering chemotherapy at full dose and on schedule is limited primarily by myelosuppression. To determine how expert opinion about preferred chemotherapy for lung, breast, and colorectal cancers has changed over the past decade, the National Comprehensive Cancer Network (NCCN) treatment guidelines from 1996, 2000 or 2001, and 2005 for each tumor type were compared. The myelosuppressive potentials of NCCN-recommended agents were assessed using data from their prescribing information. Many agents and combinations of agents recommended in the NCCN guidelines for treating lung, breast, and colorectal cancers are associated with myelosuppression. Several of these myelosuppressive regimens, which were previously recommended for treating advanced-stage or metastatic disease, are now preferred for early-stage disease, and neoadjuvant or adjuvant therapy is now recommended in more tumor types and stages than ever before. These findings indicate that the cytotoxic agents and regimens recommended today are associated with more myelosuppression than those preferred a decade ago and are more widely used in early-stage disease when survival benefits are possible. Because of this trend toward more intensive treatment of patients with cancer, proactive steps should be taken to minimize the risk for myelosuppression and its complications while optimizing the relative dose intensity. (*JNCCN* 2006;4:649–658)

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Submitted April 25, 2005; accepted for publication January 18, 2006.

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Lung, breast, and colorectal cancers are the major causes of cancer-related death in the United States. They are the top 3 causes of cancer death in women and 2 of the top 3 in men.[1] An estimated 258,210 Americans died from these cancers in 2005, accounting for more than 700 deaths per day.[1] The mortality rates in each of these tumor types, however, have declined significantly in the past 15 years.[2] Most patients diagnosed with localized breast or colorectal cancer are still alive at 5 years (98% and 90%, respectively), but the 5-year survival rates are lower in disease with distant metastases (26% and 10%, respectively).[2] Only 16% of lung cancers are detected at an early stage, when the 5-year survival rate is 49%.[2] Because most patients present with advanced or non-small cell lung cancer (NSCLC), for which effective treatment is lacking,[3,4] 1-year survival rates are more commonly reported in lung cancer. Similar to those of breast and colorectal cancers, however, 1-year survival rates for all lung cancer histologies combined increased from 37% in 1975 to 42% in 1998.[2]

This increase in survival rates for these patients may have occurred for many reasons. In breast and colorectal cancers, the increase may be attributed partially to the greater detection of early-stage disease. The appropriate use of mammography and colorectal cancer screening tests (such as fecal occult blood tests) has enabled early detection and removal of small tumors, potentially preventing progression to invasive disease. Conversely, the limited success in increasing survival of patients with lung cancer may be attributed to the absence of sensitive tests for early detection.[2]

Advances in treatment options have also contributed to the greater survival in patients with lung, breast, and colorectal cancers.[2] Various treatment options are available depending on the type and stage of the disease; however, chemotherapy remains the cornerstone of treatment for each tumor type. More effective combinations of agents and dosing schedules for early- and advanced-stage disease may also contribute to higher survival rates.

Maintaining chemotherapy dose intensity is crucial for greater survival in the curative setting in chemosensitive cancers such as early-stage breast cancer,[5–8] and for optimal treatment outcomes in the noncurative setting in patients with metastatic breast cancer,[9] metastatic colorectal cancer,[10,11] and small cell lung cancer.[12] However, chemotherapy dose attenuations are common in community oncology practice. For example, in 2 recent nationwide surveys of patients treated with potentially curative chemotherapy for early-stage breast cancer (N = 20,799)[13] and non-Hodgkin's lymphoma (N = 4522),[14] approximately half were treated with a relative dose intensity (RDI) less than 85% of the reference standard dose. In both surveys, more than half of the overall reduction in average RDI was unplanned and was associated with dose reductions and treatment delays.

The primary cause of unplanned dose reductions or treatment delays is myelosuppression, specifically grades 3 and 4 neutropenia (neutrophil count < 1×10^9/L), anemia (hemoglobin < 8 g/dL), and thrombocytopenia (platelet count < 50×10^9/L).[15–21] Managing myelosuppression is therefore crucial to maintaining RDI.

To explore the evolution of chemotherapy and advances in the standard of care for lung, breast, and colorectal cancers in the past decade, changes in the preferred regimens were evaluated and the hematologic toxicity of those regimens was reported. Ongoing clinical trials of chemotherapy regimens in these tumor types were also reviewed for an indication of future treatment directions. This report is limited to changes in chemotherapy and does not consider other treatment modalities, such as surgery, radiotherapy, and targeted therapies.

Methods and Data Reviewed

To determine how the treatment of lung, breast, and colorectal cancers has changed, the National Comprehensive Cancer Network (NCCN) treatment guidelines from 1996, 2000 or 2001, and 2005 for each tumor type were compared.[22–32] The data in this article are limited to category 1 and category 2A recommendations. Category 1 recommendations are those with uniform panel consensus, based on high-level evidence, and category 2A recommendations are those with uniform panel consensus based on lower-level evidence, including clinical experience.

To determine the myelosuppressive potential of agents included in the guidelines, the data from clinical trials in the prescribing information for those agents were reviewed. Table 1 summarizes the hematologic toxicity of chemotherapy agents that have been in use since 1990. This table does not include drugs approved before 1974 for which prescribing information was not available online (leucovorin, methotrexate, cyclophosphamide, fluorouracil, vincristine, vinblastine), nor does it include drugs approved between 1974 and 1989 that were not tested in the tumor types of interest (doxorubicin, cisplatin, etoposide, ifosfamide, carboplatin). Targeted agents (bevacizumab and erlotinib) are also excluded.

To determine future trends, regimens that are currently being tested in clinical trials (active randomized phase III studies of chemotherapy in lung, breast, and colorectal cancers, sponsored by the National Cancer Institute [NCI] and listed on www.cancer.gov/clinical_trials) were identified and evaluated.

Highly Myelosuppressive Modern Chemotherapy Regimens

Many agents listed as preferred in the NCCN guidelines are myelosuppressive, such as the taxanes, which have been approved for treating advanced-stage lung cancer[3,12] and most stages of breast cancer.[27,28] The incidence of grade 3 or 4 neutropenia with docetaxel monotherapy was 65% in previously treated patients with metastatic or recurrent lung cancer and 86% in those with metastatic or recurrent breast cancer.[37] The incidences of grade 4 neutropenia in patients with metastatic recurrent breast cancer treated with 2 different doses of paclitaxel monotherapy were 19% and 28%[35] (Table 1). Paclitaxel and docetaxel, along with gemcitabine and vinorelbine, are components of first-line platinum-based therapy in metastatic or recurrent NSCLC.[3,12] When they were combined with cisplatin in this setting, the incidence of grade 3 or 4

Table 1 Hematologic Toxicities Reported in the Prescribing Information for Chemotherapy Agents In* Use After 1990 and Recommended for the Treatment of Lung, Colorectal, and Breast Cancers

			Incidence of grade 3 or 4 (grade 4 only), %†		
Drug	**Disease setting**	**Regimen**	**Neutropenia**	**Anemia**	**Thrombocytopenia**
Pemetrexed[33]	Stage III or IV NSCLC, previously treated with chemotherapy	Pemetrexed 500 mg/m² IV over 10 min q3wk (*n* = 265)	5 (2)	8 (2)	2 (0)
Pegylated liposomal doxorubicin[34]	Chemotherapy-naïve, advanced breast cancer	Pegylated liposomal doxorubicin 50 mg/m² q4wk (*n* = 254)	0	1	0
Paclitaxel[35]	Metastatic breast cancer, second- or third-line therapy	Paclitaxel 175 mg/m² IV over 3 hours (*n* = 229)	(28)	4	3
		Paclitaxel 135 mg/m² IV over 3 hours (*n* = 229)	(19)	2	2
	Node-positive breast cancer, adjuvant therapy	Cyclophosphamide 600 mg/m², doxorubicin 60, 75, or 90 mg/m² plus G-CSF q3wk × 4 followed by paclitaxel 175 mg/m² q3wk × 4 (*n* = 1570)	(50)	6	11
	NSCLC, first-line therapy	Paclitaxel 135 mg/m² IV over 24 h with cisplatin 75 mg/m² (*n* = 195)	(75)	22	6
		Paclitaxel 250 mg/m² IV over 24 h with cisplatin 75 mg/m² plus G-CSF (*n* = 197)	(65)	19	12
Vinorelbine[36]	Stage III or IV NSCLC, first-line therapy	Vinorelbine 30 mg/m²/wk (*n* = 206)	53 (28)	NR	0
		Vinorelbine 30 mg/m²/wk plus cisplatin 120 mg/m² days 1 and 29 then q6wk (*n* = 206)	78 (58)	NR	4 (1)‡
	Stage IIIB or IV NSCLC, first-line therapy	Vinorelbine 25 mg/m²/wk plus cisplatin 100 mg/m² q4wk (*n* = 212)	82 (60)	24 (3)	5 (1)‡
Docetaxel[37]	Metastatic or locally advanced breast cancer, second-line therapy	Docetaxel 100 mg/m² IV over 1 h q3wk (*n* = 965)	86	8	NR
	Metastatic or locally advanced NSCLC, previously treated with platinum-based chemotherapy	Docetaxel 75 mg/m² (*n* = 176)	65	9	3
	Unresectable stage IIIB or IV NSCLC, first-line therapy	Docetaxel 75 mg/m² plus cisplatin 75 mg/m² (*n* = 406)	74	7	3
Gemcitabine[38]	Metastatic or locally advanced NSCLC, first line therapy	Gemcitabine 1000 mg/m²/wk × 3 q4wk plus cisplatin 100 mg/m² q4wk (*n* = 217–253)	57 (35)	25 (3)	50 (25)
Irinotecan[39]	Metastatic colorectal cancer, first-line therapy	Irinotecan 125 mg/m²/wk × 4 q6wk (*n* = 223)	31 (12)	5	2
		Irinotecan 125 mg/m² + bolus fluorouracil-leucovorin 500 and 20 mg/m²/wk × 4 q6wk (*n* = 225)	54 (24)	8	3

Table 1 Continued

		Irinotecan 125 mg/m² plus fluorouracil-leucovorin IV days 1 and 2 q2wk (*n* = 145)	46	2	0
	Metastatic colorectal cancer, second-line therapy after prior fluorouracil	Irinotecan 125 mg/m²/wk × 4 q6wk	26 (12)	7	All grades <10%
		Irinotecan 350 mg/m² q3wk (2 unpooled trials: n = 189, *n* = 127)	22, 14	7, 6	1, 4
Topotecan[40]	Recurrent or progressive small-cell lung cancer	Topotecan 1.5 mg/m²/d × 5 q3wk (*n* = 107)	(70)	42	(29)[†]
Capecitabine[41]	Metastatic colorectal cancer, first-line therapy	Capecitabine 1250 mg/m² bid × 2 wk q3wk (*n* = 596)	3 (2)	3 (1)	All grades <5%
	Stage IV metastatic breast cancer	Monotherapy as above (*n* = 162)	4 (2)	4 (1)	4 (1)
	Metastatic breast cancer, previously treated with anthracyclines	Capecitabine 1250 mg/m² bid × 2 wk q3wk × 6 plus docetaxel 75 mg/m² q3wk × 6 (*n* = 251)	69 (49)	10 (3)	3 (1)
Epirubicin[42]	Node-positive stage II or III breast cancer, adjuvant therapy	Pooled data from 2 trials of epirubicin 100 or 120 mg/m² (*n* = 620):	67	6	5
		Fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 100 mg/m² IV q3wk × 6 (FEC100)			
		OR			
		Oral cyclophosphamide 75 mg/m² × 14 d q4wk × 6; epirubicin 60 mg/m²/wk, fluorouracil 500 mg/m²/wk IV for 2 wk q4wk × 6 (CEF120)			
		Fluorouracil 500 mg/m², epirubicin 50 mg/m², cyclophosphamide 500 mg/m² IV q3wk × 6 (FEC50) (*n* = 280)	11	0	0
Oxaliplatin[43]	Advanced, relapsed, or refractory colorectal cancer	Oxaliplatin 85 mg/m² IV over 2 h q2wk (*n* = 153)	0	1	3
		FOLFOX4:			
		Oxaliplatin 85 mg/m² IV over 2 h on day 1 plus leucovorin 200 mg/m² IV over 2 h followed by fluorouracil 400 mg/m² bolus and 600 mg/m² IV over 22 h on days 1 and 2 q2wk (*n* = 150)	44	2	4
	Advanced colorectal cancer, first-line therapy	Oxaliplatin 85 mg/m² IV over 2 h plus irinotecan 200 mg/m² IV over 30 min, q3wk (*n* = 264)	36	3	4
		FOLFOX4: dosages as above (*n* = 267)	53	3	5

*Drugs are listed as possible agents for treating lung, breast, or colorectal cancers in 2005 versions of NCCN Clinical Practice Guidelines in Oncology (updates may be available; see www.nccn.org). Data are limited to those from drugs approved between 1974 and 1990, tested in the cancers discussed, and for which trials include details on regimen dosages and exclude targeted agents erlotinib and bevacizumab.
Abbreviations: G-CSF, granulocyte colony-stimulating factor; IV, intravenous; NR, not reported; NSCLC, non–small cell lung cancer.
[†]Unless otherwise stated, the toxicity grades are those of the NCI Common Toxicity Criteria[21]: neutropenia (granulocytopenia: grade 3 and 4, neutrophils <1 × 10⁹/L; grade 4, <0.5 × 10⁹/L); anemia (grades 3 and 4, hemoglobin <8 g/dL; grade 4, <6.5 g/dL); thrombocytopenia (grade 3 and 4, platelets <50 × 10⁹/L; grade 4, <10 × 10⁹/L).
[‡]SWOG and WHO criteria: grade 4, platelets <25 × 10⁹/L.

neutropenia was 75% with paclitaxel (grade 4 only),[35] 74% with docetaxel,[37] 57% with gemcitabine,[38] and 72% to 82% with vinorelbine.[36] Approximately 25% of patients treated with the gemcitabine- and vinorelbine-platinum regimens experienced grade 3 or 4 anemia[36,38] (Table 1).

Regimens that combine fluorouracil and leucovorin with the newer agents irinotecan (FOLFIRI) and oxaliplatin (FOLFOX) are used for adjuvant and first- and second-line salvage treatment of metastatic or recurrent colorectal cancer. The rate of grade 3 or 4 neutropenia in previously untreated patients with advanced disease was 53% with FOLFOX and 54% with FOLFIRI (Table 1).

Chemotherapy Recommended in More Disease Stages

The current trend is toward treating cancer with myelosuppressive chemotherapy earlier in the course of the disease. New agents and regimens that first emerged as standard care in metastatic or recurrent disease are now approved for early-stage disease in the adjuvant and neoadjuvant settings.

Adjuvant chemotherapy for NSCLC was not standard treatment even 5 years ago, but platinum-based regimens that have been used in patients with metastatic or recurrent disease for more than a decade are now recommended in most patients with resectable NSCLC. These changes are based on data from the prospective trial of the International Adjuvant Lung Cancer Trial Collaborative Group, involving 1867 patients with stage I to III disease, that showed slightly (4 to 5 percentage points) but significantly greater survival with adjuvant chemotherapy than with surgery alone.[44] Additional support for adjuvant chemotherapy versus surgery for NSCLC comes from 2 large prospective studies in patients with stage I or II disease, in which overall survival at 4 years was 12 percentage points higher with platinum-based chemotherapy after surgery in one trial and 15 percentage points higher at 5 years in the other.[45,46]

The advantages of adjuvant chemotherapy for breast cancer over mastectomy alone are well established.[47] The standard of care has evolved from cyclophosphamide, methotrexate, and fluorouracil (CMF) to anthracycline-based regimens to more-intensive dose-dense or taxane-based regimens such as docetaxel, doxorubicin, and cyclophosphamide (TAC). The TAC regimen, which was associated with better outcomes but higher rates of febrile neutropenia (FN) than FAC (TAC with fluorouracil instead of docetaxel) in the metastatic setting,[48] has become a preferred regimen for adjuvant chemotherapy in stage III and node-positive stage II disease.[49] Compressed administration schedules recommended in node-positive early-stage breast cancer with doxorubicin, cyclophosphamide, and sequential paclitaxel, given in 14-day treatment cycles with granulocyte colony-stimulating factor (G-CSF), are also more myelosuppressive.[50]

The FOLFOX regimen, once preferred only in the metastatic setting, is now recommended for adjuvant therapy in stage III colon cancer and stage II or III rectal cancer.[51] Data from the European MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial showed that 3-year disease-free survival was significantly higher with the addition of oxaliplatin to the fluorouracil-leucovorin regimen (FOLFOX4) (77.8% vs. 72.9%; $P = .002$) in patients with resected stage II or III colon cancer.[51] The value of adjuvant therapy in stage III colon cancer is clear, but its role in stage II colon cancer is less certain, partly because of contradictory findings in 2 large studies.[52,53] Investigators at the Mayo Clinic recently performed a meta-analysis of data on 3302 patients in 7 randomized trials and concluded that patients with stage II disease could benefit from adjuvant therapy, but to a lesser degree than patients with stage III disease.[54] These findings were confirmed by the results of the QUASAR (The Quick And Simple And Reliable) study in 3239 patients with colorectal cancer, 92% of whom had stage II disease.[55] After 5 years, adjuvant chemotherapy with 5-fluorouracil and folinic acid with or without levamisole was associated with a 22% reduction in the risk for recurrence ($P = .001$) and a 17% reduction in the risk for death ($P = .02$) compared with observation alone. Thus adjuvant chemotherapy showed a small but definite survival advantage with chemotherapy in stage II colon cancer.

Neoadjuvant chemotherapy is now recommended in many more treatment settings than before. Neoadjuvant chemotherapy with concurrent radiotherapy is recommended in an increasing number of tumor stages and classifications of NSCLC. Although still considered optional for breast cancer, as in the

adjuvant setting, the preferred regimens are now more myelosuppressive than earlier regimens. Neoadjuvant chemotherapy was considered optional in rectal cancer 5 years ago, but is now recommended in all lymph node–positive disease and node-negative T3 or T4 disease.

Improvement in Long-Term Clinical Outcomes With Myelosuppressive Regimens

The regimens with the best long-term outcomes are also highly myelosuppressive. Historically, the role of chemotherapy in advanced NSCLC was only palliative; it was prescribed primarily to lessen symptoms and improve quality of life.[56] A decade ago, meta-analyses showed only slightly greater survival with cisplatin-based chemotherapy than with supportive care,[57–59] and the 1-year survival rates typically ranged from 10% to 25%.[56,60–64] Newer chemotherapy regimens (e.g., taxane combinations, gemcitabine, vinorelbine, irinotecan, topotecan with platinum compounds) are highly myelosuppressive but routinely produce median survival rates of 8 to 10 months and 1-year survival rates of 30% to 40% in metastatic NSCLC.[65] Furthermore, in recent trials in which survival was greater with adjuvant chemotherapy than with surgery alone in NSCLC, grade 4 neutropenia was common, with reported rates of 17.5%[44] and 25%.[45]

Similar trends have been seen in breast cancer. The overall response rate in metastatic breast cancer was significantly higher with first-line TAC than with FAC (55% vs. 44%; $P = .02$), but grade 3 or 4 neutropenia (94% vs. 81%) and FN (29% vs. 5%) were also more common.[48] In the adjuvant setting, the 5-year disease-free survival rate was significantly higher with TAC than with FAC (75% vs. 68%; $P = .001$), as was the 5-year overall survival rate (87% vs. 81%; $P = .008$), but the incidences of FN (24% vs. 2%) and grade 3 or 4 infection (3% vs. 1%) were also higher.[49] Also in the adjuvant setting, the 3-year disease-free survival (85% vs. 81%; $P = .01$) and overall survival rates (92% vs. 90%; $P = .01$) were higher with 14-day than with 21-day cycles of doxorubicin, cyclophosphamide, and paclitaxel. However, because the 14-day regimens are not feasible without G-CSF support, its use with those regimens was required in the study protocol.[50]

The addition of oxaliplatin to fluorouracil-leucovorin in patients with previously untreated advanced colorectal cancer was associated with longer disease-free survival (median, 9.0 vs. 6.2 months; $P < .001$) and a higher response rate (50.7% vs. 22.3%; $P = .001$). The higher rate of grade 3 or 4 neutropenia (41.7% vs. 5.3%) was not associated with a decrease in quality of life.[66] Similarly, in the adjuvant setting in patients with resected stage II or III colon cancer, the 3-year disease-free survival rate was higher with FOLFOX4 than with fluorouracil-leucovorin (78% vs. 73%; $P = .002$), but the rate of grade 3 or 4 neutropenia was significantly greater (41% vs. 5%; $P < .001$).[51]

Hematopoietic Support for Myelosuppressive Regimens

Increased myelosuppression with new combinations of agents creates a greater need for supportive care. Phase III studies have shown that chemotherapy-induced neutropenia[67–70] and anemia[71–73] can be prevented or managed with growth factors. G-CSF is typically required in the first chemotherapy cycle to manage myelosuppression that would otherwise be dose-limiting. Using G-CSF in response to an episode of FN is not appropriate, because almost three quarters of all episodes of severe neutropenia, and more than half of all episodes of FN, occur in the first cycle of chemotherapy.[74,75] National practice guidelines recommend that patients at high risk for neutropenia and its complications, including those aged 65 years or older, be given G-CSF in all cycles of myelosuppressive chemotherapy.[17,76]

As a result of findings in clinical trials, G-CSF has become an integral component of modern chemotherapy regimens. For example, after the success of TAC in node-positive breast cancer,[49] Martin et al.[77] conducted a trial of TAC in node-negative breast cancer. After 224 patients had been enrolled, the protocol was amended to mandate G-CSF in the TAC arm but not the FAC arm. The incidence of FN in patients in the TAC arm was reduced from 23.8% before the protocol amendment to only 3.5% after the amendment—a rate closer to that in the FAC arm (1.3%).

In dose-dense (14-day) adjuvant therapy for early-stage breast cancer, neutrophil counts cannot recover sufficiently without G-CSF support to allow the delivery of the next cycle of chemotherapy on schedule.[50,78] Consequently, G-CSF is required for this chemotherapy regimen to be feasible.[50,78] In one study,

dose reductions and treatment delays were less frequent in the dose-dense arms (14-day) compared with the control arms (21-day), with hematologic toxicity causing 38% of the cycle delays in the 21-day regimens but only 15% of the delays in the 14-day regimens ($P < .001$).[50] The dose-dense arms of these trials were also associated with a higher rate of anemia. Red blood cell transfusions were required in 13% of the patients in the dose-dense arms, possibly because of grade 2 anemia.[50] However, the transfusion rate was 0% with the same 14-day regimen when darbepoetin alfa was initiated because hemoglobin levels fell below 12 g/dL.[79]

Maintenance of standard chemotherapy dose intensity is associated with optimal disease-free and overall survival in early-stage breast cancer.[5–8] Therefore, appropriate supportive care may be particularly important to ensure that full-dose chemotherapy is delivered on schedule in the adjuvant and neoadjuvant settings, in which chemotherapy is used with curative intent. Using less myelosuppressive regimens (e.g., weekly schedules or dose reductions) may be acceptable in palliative settings.

The potential effect of dose intensity on the treatment outcomes in adjuvant therapy for NSCLC and colorectal cancer has received little attention. In 2 recent trials of adjuvant therapy for NSCLC that did not include prophylactic G-CSF, dose delays or reductions occurred in all patients treated with cisplatin plus vinorelbine (with 74% of the reductions caused by neutropenia),[46] and the full dose of cisplatin plus paclitaxel for 4 cycles was delivered in only 55% of patients.[45] In patients with colorectal cancer (in which grade 3 or 4 neutropenia and thrombocytopenia were managed by dose reductions or delays) enrolled in the MOSAIC trial, 80.5% of the planned oxaliplatin dose and 84.4% of the planned fluorouracil dose were given across all cycles in the FOLFOX4 arm and 97.7% of the planned fluorouracil dose was given in the fluorouracil-leucovorin arm.[51] Further data are required to determine whether closer adherence to the planned dose and schedule is important for optimal treatment outcomes in the adjuvant setting in NSCLC and colorectal cancer.

Evaluating the need for erythropoietin support in patients with lung cancer whose hemoglobin levels are less than 11 g/dL may be particularly important.[80] Pretreatment anemia is prevalent in patients with lung cancer, is multifactorial in origin, and is caused by factors such as impaired iron utilization, poor nutritional status, hypoplasia of the bone marrow, and inappropriate levels of erythropoietin.[81] Underlying pulmonary disease may also contribute to the greater functional disability caused by anemia in patients with lung cancer.[19] In older patients who are treated with myelosuppressive chemotherapy, anemia-related fatigue may precipitate functional dependence.[82] Retrospective studies have shown that, among patients with solid tumors, blood transfusions for anemia are most common in those with lung cancer.[83,84] In addition to the myelosuppressive potential of the preferred agents used in lung cancer, cisplatin is also associated with damage to the renal tubules, which adversely affects the production of erythropoietin.[85] Because anemia is associated with a poor prognosis for survival and positive treatment outcomes in lung cancer,[20] its management should be an essential component of lung cancer treatment.[81]

In 1991, Dische[86] found that 23 of 25 studies reported an adverse influence of anemia on the outcomes in patients with various tumors treated with radiotherapy. More recent studies show that anemia before or during radiotherapy is associated with poor locoregional control and lower survival rates in patients with advanced head and neck cancer, carcinoma of the cervix, or ovarian cancer.[87–90] Therefore, correction of anemia may be important when radiotherapy is used concurrently with or after chemotherapy.

Ongoing Clinical Trials in Lung, Breast, and Colorectal Cancers

Myelosuppressive drugs are a component of many regimens now in clinical trials, indicating a continuing role in systemic therapy for lung, breast, and colorectal cancers.[91] Taxane-based regimens, for example, are used in 8 of 10 active NCI-sponsored trials in breast cancer and are being studied in the neoadjuvant, adjuvant, and metastatic settings. Furthermore, taxanes in combination with gemcitabine and carboplatin are being evaluated as first-line therapy for advanced NSCLC in 2 active NCI-sponsored trials (ALPHA-A1-99002L and CWRU-LILY-1503).

Myelosuppressive chemotherapy agents and regimens are also being evaluated in combination with other anticancer agents, including new biologic agents. For example, studies are evaluating FOLFOX and

FOLFIRI with or without cetuximab in resectable colon cancer (NCCTG-N0147) and metastatic colorectal cancer (CALGB-80203). FOLFOX is also being evaluated in combination with PTK787/ZK 222584 (an investigational angiogenesis inhibitor) in metastatic colorectal cancer (UCLA-0304011).

Numerous ongoing trials are focusing on determining the optimal dosing schedules of additional myelosuppressive regimens, especially in early-stage breast cancer in which dose intensity may affect survival. The investigational schedules in operable breast cancer include dose-dense (14-day) cycles of adjuvant doxorubicin plus cyclophosphamide followed by paclitaxel, with or without gemcitabine, with hematopoietic support (SWOG-S0221, NSASP-B-38).

Additional studies are exploring adjuvant or neoadjuvant therapy with currently preferred agents earlier in the course of the disease and in patients with a poor performance status. For example, capecitabine, a preferred agent for stage IV colorectal and breast cancers, is being tested as adjuvant therapy in colon cancer (UCLA-0310023), neoadjuvant therapy in rectal cancer (NSABP-R-04, ECOG-E3201), and adjuvant therapy in breast cancer in older women (CALGB-49907). The combination of docetaxel and infliximab is being studied in patients with advanced NSCLC who have a poor performance status (for whom best supportive care is currently recommended) and in elderly patients (NCCTG-N01C9).

Conclusions

Although advances in chemotherapy regimens have increased survival in patients with lung, breast, and colorectal cancers, they are also associated with substantial increases in myelosuppression. The chemotherapy regimens recommended in the NCCN guidelines for these cancers are associated with a high incidence and severity of neutropenia and anemia. Furthermore, results of clinical trials have led experts to recommend the use of adjuvant or neoadjuvant therapy with myelosuppressive agents in more disease stages than before. Ongoing trials suggest that myelosuppressive drugs will continue to have a role in cancer treatment. Because myelosuppression frequently results in reduced chemotherapy dose intensity that can have a substantial negative impact on survival, supportive care must be provided with chemotherapy. As oncologists increase their use of these more intensive treatments, they should consider appropriate hematopoietic support to manage myelosuppression and help ensure the delivery of full-dose chemotherapy on schedule.

References

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10–30.
2. American Cancer Society. Cancer Facts and Figures 2005. Atlanta, GA: American Cancer Society; 2005.
3. Ettinger DS, Argiris A, Bepler G, et al. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines, version 2, 2006. Available at: http: //www.nccn.org. Accessed May 23, 2006.
4. Kim ES, Vokes EE, Kies MS. Cetuximab in cancers of the lung and head & neck. Semin Oncol 2004;31(suppl 1):61–67.
5. Hryniuk W, Levine MN. Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. J Clin Oncol 1986;4: 1162–1170.
6. Bonadonna G, Valagussa P, Moliterni A, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. N Engl J Med 1995;332: 901–906.
7. Budman DR, Berry DA, Cirrincione CT, et al. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. J Natl Cancer Inst 1998;90: 1205–1211.
8. Mayers C, Panzarella T, Tannock IF. Analysis of the prognostic effects of inclusion in a clinical trial and of myelosuppression on survival after adjuvant chemotherapy for breast carcinoma. Cancer 2001; 91:2246–2257.
9. Hryniuk W, Frei E III, Wright FA. A single scale for comparing dose-intensity of all chemotherapy regimens in breast cancer: summation dose-intensity. J Clin Oncol 1998;16:3137–3147.
10. Jakobsen A, Berglund A, Glimelius B, et al. Dose-effect relationship of bolus 5-fluorouracil in the treatment of advanced colorectal cancer. Acta Oncol 2002;41:525–531.
11. Scheithauer W, Kornek GV, Raderer M, et al. Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2003;21:1307–1312.
12. Johnson BE, Argiris A, Crawford J, et al. The NCCN Small Cell Lung Cancer Clinical Practice Guidelines, version 1, 2006. Available at: http://www.nccn.org. Accessed May 23, 2006.
13. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol 2003;21: 4524–4531.
14. Lyman GH, Dale DC, Friedberg J, et al. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. J Clin Oncol 2004;22:4302–4311.
15. Cairo MS. Dose reductions and delays: limitations of myelosuppressive chemotherapy. Oncology 2000;14(suppl 8):21–31.
16. Chang J. Chemotherapy dose reduction and delay in clinical practice: evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer. Eur J Cancer 2000;36(suppl 1): S11–S14.
17. Ozer H, Armitage JO, Bennett CL, et al. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society

of Clinical Oncology Growth Factors Expert Panel. J Clin Oncol 2000; 18:3558–3585.

18. Link BK, Budd GT, Scott S, et al. Delivering adjuvant chemotherapy to women with early-stage breast carcinoma: current patterns of care. Cancer 2001;92:1354–1367.
19. Scagliotti GV, Novello S. Role of erythropoietin in the treatment of lung cancer associated anaemia. Lung Cancer 2001;34(suppl 4): S91–S94.
20. Pirker R, Wiesenberger K, Pohl G, Minar W. Anemia in lung cancer: clinical impact and management. Clin Lung Cancer 2003;5:90–97.
21. National Cancer Institute. Cancer Therapy Evaluation Programs, Common Toxicity Criteria Manual. Version 2.0; June 1, 1999. Available at: http://ctep.cancer.gov/forms/CTCManual_v4_10-4-99.pdf. Accessed June 13, 2006.
22. Demetri G, Elias A, Gershenson D, et al. NCCN Small-Cell Lung Cancer Practice Guidelines.™ The National Comprehensive Cancer Network. Oncology (Huntingt) 1996;10(11 suppl):179–194.
23. Ettinger DS, Cox, JD, Ginsberg RJ, et al. NCCN Non-Small-Cell Lung Cancer Practice Guidelines.™ The National Comprehensive Cancer Network. Oncology (Huntingt) 1996;10(11 suppl):81–111.
24. Ettinger DS, Kris MG, NCCN Non-Small Cell Lung Cancer Practice Guidelines™ Panel. NCCN: Non-small cell lung cancer. Cancer Control 2001;8(suppl 2):22–31.
25. Johnson BE, NCCN Small Cell Lung Cancer Practice Guidelines Panel. NCCN: small cell lung cancer. Cancer Control 2001; 8(6 suppl 2):32–43.
26. Carlson RW, Goldstein LJ, Gradishar WJ, et al. NCCN Breast Cancer Practice Guidelines.™ The National Comprehensive Cancer Network. Oncology (Huntingt) 1996;10(11 suppl):47–75.
27. Carlson RW, Anderson BO, Bensinger W, et al. NCCN Breast Cancer Clinical Practice Guidelines, version 1, 2005. Available at: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed May 23, 2006.
28. Carlson RW, Anderson BO, Bensinger W, et al. NCCN Practice Guidelines for Breast Cancer. Oncology (Huntingt) 2000;14:33–49.
29. Engstrom PF, Benson AB III, Cohen A, et al. NCCN Colorectal Cancer Practice Guidelines. The National Comprehensive Cancer Network. Oncology (Huntingt) 1996;10(11 suppl):140–175.
30. Engstrom PF, Benson AB III, Chen Y-J, et al. NCCN Colon Cancer Clinical Practice Guidelines, version 2, 2005. Available at: http://www.nccn.org/ professionals/physician_gls/PDF/colon.pdf. Accessed May 23, 2006.
31. Engstrom PF, Benson AB III, Chen Y-J, et al. NCCN Rectal Cancer Clinical Practice Guidelines, version 1, 2005. Available at: http://www.nccn.org/professionals/physician_gls/PDF/rectal.pdf. Accessed May 23, 2006.
32. Benson AB III, Choti MA, Cohen AM, et al. NCCN Practice Guidelines for Colorectal Cancer. Oncology (Huntingt) 2000;14: 203–212.
33. Alimta [package insert]. Indianapolis, IN; Eli Lilly & Co; 2004.
34. Caelyx [package insert]. Bruxelles, Belgium; SP Europe; 2005.
35. Taxol [package insert]. Princeton, NJ: Bristol-Meyers Squibb Co; 2003.
36. Navelbine [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2003.
37. Taxotere [package insert]. Bridgewater, NJ: Aventis Pharmaceuticals; 2004.
38. Gemzar [package insert]. Indianapolis, IN: Eli Lilly & Co; 2004.
39. Camptosar [package insert]. New York, NY: Pfizer Inc; 2004.
40. Hycamtin [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2003.
41. Xeloda [package insert]. Nutley, NJ: Roche Pharmaceuticals; 2003.
42. Ellence [package insert]. Kalamazoo, MI: Pharmacia & Upjohn; 2003.
43. Eloxatin [package insert]. New York, NY: Sanofi-Synthelabo; 2004.
44. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351–360.
45. Strauss GM, Herndon J, Maddaus MA, et al. Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): report of Cancer and Leukemia Group B (CALGB) protocol 9633 [Abstract]. Presented at the 40th Annual Meeting of the American Society of Clinical Oncology; June 5–8, 2004; New Orleans, LA. Abstract #7019.
46. Winton TL, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non small cell lung cancer. N Engl J Med 2005;352:2589–2597.
47. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998;352:930–942.
48. Mackey JR, Paterson A, Dirix LY, et al. Final results of the phase III randomized trial comparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) to FAC as first line chemotherapy (CT) for patients (pts) with metastatic breast cancer (MBC) [Abstract]. Proc Am Soc Clin Oncol 2002;21:35a. Abstract #137.
49. Martin M, Pienkowski T, Mackay J, et al. TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up [abstract 43]. Presented at the 26th Annual San Antonio Breast Cancer Symposium; December 3–6, 2003; San Antonio, TX. Abstract #43.
50. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup trial C9741/Cancer and Leukemia Group B trial 9741. J Clin Oncol 2003;21:1431–1439. [erratum in J Clin Oncol 2003;21: 2226].
51. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343–2351.
52. Mamounas E, Wieand S, Wolmark N, et al. Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B versus Dukes' C colon cancer: results from four National Surgical Adjuvant Breast and Bowel Project adjuvant studies (C-01, C-02, C-03, and C-04). J Clin Oncol 1999;17:1349–1355.
53. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. J Clin Oncol 1999;17:1356–1363.
54. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22:1797–1806.
55. Gray RG, Barnwell J, Hills R, et al. QUASAR: a randomized study of adjuvant chemotherapy (CT) vs observation including 3238 colorectal cancer patients [Abstract]. Proc Am Soc Clin Oncol 2004;23:246. Abstract #3501.
56. Cullen MH, Billingham LJ, Woodroffe CM, et al. Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. J Clin Oncol 1999;17:3188–3194.
57. Marino P, Pampallona S, Preatoni A, et al. Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. Chest 1994;106:861–865.

58. Grilli R, Oxman AD, Julian JA. Chemotherapy for advanced non-small-cell lung cancer: how much benefit is enough? J Clin Oncol 1993;11:1866–1872.
59. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995;311:899–909.
60. Bonomi PD, Finkelstein DM, Ruckdeschel JC, et al. Combination chemotherapy versus single agents followed by combination chemotherapy in stage IV non-small-cell lung cancer: a study of the Eastern Cooperative Oncology Group. J Clin Oncol 1989;7:1602–1613.
61. Gandara DR, Crowley J, Livingston RB, et al. Evaluation of cisplatin intensity in metastatic non-small-cell lung cancer: a phase III study of the Southwest Oncology Group. J Clin Oncol 1993;11:873–878.
62. Klastersky J, Sculier JP, Bureau G, et al. Cisplatin versus cisplatin plus etoposide in the treatment of advanced non-small-cell lung cancer. Lung Cancer Working Party, Belgium. J Clin Oncol 1989;7:1087–1092.
63. Rapp E, Pater JL, Willan A, et al. Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer—report of a Canadian multicenter randomized trial. J Clin Oncol 1988;6:633–641.
64. Ruckdeschel JC, Finkelstein DM, Ettinger DS, et al. A randomized trial of the four most active regimens for metastatic non-small-cell lung cancer. J Clin Oncol 1986;4:14–22.
65. Ettinger DS. Is there a preferred combination chemotherapy regimen for metastatic non-small cell lung cancer? Oncologist 2002;7:226–233.
66. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938–2947.
67. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991;325:164–170.
68. Trillet-Lenoir V, Green J, Manegold C, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. Eur J Cancer 1993;29A:319–324.
69. Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 2002;20:727–731.
70. Green MD, Koelbl H, Baselga A, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol 2003;14:29–35.
71. Del Mastro L, Venturini M, Lionetto R, et al. Randomized phase III trial evaluating the role of erythropoietin in the prevention of chemotherapy-induced anemia. J Clin Oncol 1997;15:2715–2721.
72. Dunphy FR, Harrison BR, Dunleavy TL, et al. Erythropoietin reduces anemia and transfusions: a randomized trial with or without erythropoietin during chemotherapy. Cancer 1999;86:1362–1367.
73. Vansteenkiste J, Pirker R, Massuti B, et al. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. J Natl Cancer Inst 2002;94:1211–1220.
74. Crawford J, Wolff DA, Culakova E, et al. First cycle risk of severe and febrile neutropenia in cancer patients receiving systemic chemotherapy: results from a prospective nationwide study [Abstract]. Blood 2004;104:607a–608a. Abstract #2210.
75. Lyman GH, Morrison VA, Dale DC, et al. Risk of febrile neutropenia among patients with intermediate-grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. Leuk Lymphoma 2003;44:2069–2076.
76. National Comprehensive Cancer Network. NCCN Senior Adult Clinical Practice Guidelines, version 1, 2005. Available at:.nccn.org/professionals/physician_gls. Accessed June 13, 2006.
77. Martin M, Lluch A, Segui MA, et al. Prophylactic growth factor (GF) support with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) for node-negative breast cancer (BC): an interim safety analysis of the GEICAM 9805 study [Abstract]. Proc Am Soc Clin Oncol 2004;23:32. Abstract #620.
78. Ellis GK, Livingston RB, Gralow JR, Green SJ, Thompson T. Dose-dense anthracycline-based chemotherapy for node-positive breast cancer. J Clin Oncol 2002;20:3637–3643.
79. Burstein HJ, Parker LM, Doherty J, et al. Use of the long-acting hematopoietic growth factors pegfilgrastim and darbepoetin alfa in support of dose-dense adjuvant chemotherapy [Abstract]. Presented at the 27th Annual San Antonio Breast Cancer Symposium; December 8–11, 2004; San Antonio, TX. Abstract #1055.
80. National Comprehensive Cancer Network. NCCN Cancer and Treatment-Related Anemia Clinical Practice Guidelines, version 2, 2006. Available at: http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf. Accessed May 23, 2006.
81. Garst J. Role of erythropoietin agents in patients with lung cancer. Am Soc Clin Oncol Educ Book 2004:476-479.
82. Balducci L. Anemia, cancer, and aging. Cancer Control 2003;10:478–486.
83. Barrett-Lee PJ, Bailey NP, O'Brien ME, Wager E. Large-scale UK audit of blood transfusion requirements and anaemia in patients receiving cytotoxic chemotherapy. Br J Cancer 2000;82:93–97.
84. Skillings JR, Sridhar FG, Wong C, Paddock L. The frequency of red cell transfusion for anemia in patients receiving chemotherapy. A retrospective cohort study. Am J Clin Oncol 1993;16:22–25.
85. Wood PA, Hrushesky WJ. Cisplatin-associated anemia: an erythropoietin deficiency syndrome. J Clin Invest 1995;95:1650–1659.
86. Dische S. Radiotherapy and anaemia—the clinical experience. Radiother Oncol 1991;20(suppl 1):35–40.
87. Obermair A, Petru E, Windbichler G, et al. Significance of pretreatment serum hemoglobin and survival in epithelial ovarian cancer. Oncol Rep 2000;7:639-644.
88. Lee WR, Berkey B, Marcial V, et al. Anemia is associated with decreased survival and increased locoregional failure in patients with locally advanced head and neck carcinoma: a secondary analysis of RTOG 85-27. Int J Radiat Oncol Biol Phys 1998;42:1069–1075.
89. Grogan M, Thomas GM, Melamed I, et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. Cancer 1999;86:1528–1536.
90. Semrau R, Mueller R-P, Stuetzer H, et al. Ceiling effect of haemoglobin (HB)-levels increasing efficacy of intensified hyperfractionated (HF) and accelerated (ACC) radiotherapy (RT) and concurrent chemotherapy with carboplatin and 5-FU—updated results of a randomized multicentric German trial in advanced head and neck cancer [Abstract]. Presented at the 2004 ASTRA Annual Meeting; October 3–7, 2004; Atlanta, GA. Abstract #101.
91. National Cancer Institute. Clinical trials page. Available at: http://www.cancer.gov/clinicaltrials/findtrials. Accessed May 23, 2006.