Malignant pleural mesothelioma (MPM) is an aggressive, highly lethal neoplastic disorder of the pleural lining of the lung associated with exposure to asbestos. In the United States, about 2,000–3,000 new cases of MPM are diagnosed annually (Carbon, Kutzke, & Testa, 2002). The prognosis is dismal, with a five-year overall survival rate of about 8% in the United States (Verschraegen, 2003).

Unfortunately, MPM generally presents at an advanced stage, and the prognosis is quite poor. Median survival is brief, about 6–18 months (Carbon et al., 2002). Available treatment options include surgery, radiotherapy, cytotoxic chemotherapy, and biotherapy. However, survival outcomes remain poor, and treatment is largely palliative and limited to supportive care. Because patients with MPM typically present at advanced age and have locally advanced disease and comorbid conditions, few are candidates for surgery. Although surgery can improve recurrence-free survival and provide palliative relief of pain and discomfort for patients with early-stage disease, less than 15% of these patients survive longer than five years (Vogelzang et al., 2003). Similarly, radiotherapy has been proven to be of limited value. Although radiotherapy is useful for the palliative treatment of painful metastases, curative radiotherapy is limited by the extent of tumor volume and potential toxicity to normal tissues (Scagliotti et al., 2003).

Many cytotoxic agents, such as cisplatin, doxorubicin, and gemcitabine, have been studied as single agents and in combinations in phase II trials. Results to date with conventional agents have been disappointing. Response rates in single-agent studies typically range from 0%–15%. Median overall survival in most single-agent studies has ranged from seven to nine months. However, several studies have reported median overall survival rates from 5–11 months (Scagliotti et al., 2003).

No known cure exists for malignant pleural mesothelioma (MPM). The prognosis for patients with this relatively rare, asbestos-related malignancy of the pleural lining of the lung is quite poor. MPM treatment includes surgery, radiotherapy, and chemotherapy. Few patients, however, are candidates for surgery or radiotherapy, so chemotherapy is the only option for most patients. A phase III study found that pemetrexed and cisplatin chemotherapy significantly improved survival and had greater antitumor activity than cisplatin alone. The U.S. Food and Drug Administration recently approved pemetrexed with cisplatin for treating MPM. Nurses should become familiar with the proper preparation and administration of pemetrexed, including the necessity of supplementation with folic acid and vitamin B12. As with all drugs, careful attention must be paid to patient selection, laboratory monitoring, contraindications, and appropriate interventions in the event of adverse reactions or overdose.

Key Words: mesothelioma, antineoplastic combined chemotherapy protocols

Unsatisfactory results with conventional agents prompted increased research using newer agents with novel mechanisms of action. Perhaps the most significant new development in the treatment of MPM is the recent approval by the U.S. Food and Drug Administration (FDA) of pemetrexed (Alimta® [Eli Lilly and Company, Indianapolis, IN]), a novel multitargeted antifolate, in combination with cisplatin for front-line treatment of MPM.

Pemetrexed represents a significant advance in the treatment of MPM. Subsequent to demonstrating modest single-agent activity (response rate 14.1%; median overall survival 10.7 months) in a phase II trial of 64 patients with MPM (Scagliotti et al., 2003), pemetrexed, in combination with cisplatin, demonstrated significantly improved survival and...
overall greater antitumor activity compared to cisplatin alone in chemotherapy-naive patients with MPM (Vogelzang et al., 2003). Pemetrexed improves survival, reduces disease-related symptoms, and produces objective tumor response. Moreover, with appropriate folic acid and vitamin B₁₂ supplementation, pemetrexed offers a highly favorable toxicity profile resulting in few dose reductions or delays and a simple, brief outpatient administration schedule.

**Antifolates: A Historical Perspective**

Folic acid antagonists produced the first remissions in leukemia (Farber, Diamond, Mercer, Sylvester, & Wolff, 1948) as well as the first cure of a solid tumor, choriocarcinoma (Berlin et al., 1963). In the late 1940s, Sidney Farber, of Boston’s Children’s Hospital, observed that children with leukemia had low plasma folic acid levels. Not only was treatment with synthetic folic acid supplementation ineffective in this setting, but Farber also concluded that it actually might accelerate the course of the disease. This conclusion, which now is in doubt, led to a reevaluation of the role of folic acid in leukemia and ultimately prompted research of folic acid antagonists. Early fears that folic acid might accelerate disease progression, however, led some oncologists to advise patients to avoid supplements containing folic acid. This misconception is unfortunate because folic acid supplementation, which safely and effectively reduces antifolate toxicity without adversely affecting efficacy, has proved a valuable method of optimizing antifolate therapy (Scagliotti et al., 2003).

Over the years, antifolates have been proven useful for treating a variety of hematologic malignancies and solid tumors. The cytotoxic activity of these agents is attributed to their ability to inhibit specific folate-dependent enzymes involved in DNA synthesis. Important folic acid antagonists, or antifolates, include older agents, such as methotrexate and 5-fluorouracil, and newer agents, such as capetitabine, a novel fluoropyrimidine that is, in fact, an oral prodrug of fluorouracil. Methotrexate, a folic acid analog, is a potent inhibitor of dihydrofolate reductase (DHFR). Fluorouracil, a pyrimidine analog, inhibits thymidylate synthase (TS). Pemetrexed is unique in that it inhibits at least three important enzymes involved in folate metabolism and DNA synthesis.

**Pemetrexed**

Pemetrexed is a novel multitargeted antifolate distinguished by a unique 6–5-fused pyrrolo[2,3-D]pyrimidine nucleus that differs from the core structures of other antifolates. Pemetrexed exhibits broad antitumor activity that targets at least three metabolic enzymes involved in both pyrimidine and purine synthesis—TS, DHFR, and glycaminamide ribonucleotide formyltransferase (GARFT).

The major route for pemetrexed transport into tumor cells is the reduced folate carrier. The drug is metabolized rapidly to active polyglutamate derivatives that are potent inhibitors of enzymes critical to the synthesis of purines and thymidine. Long-term retention of the polyglutamated form of pemetrexed leads to persistently elevated intracellular concentrations and increased cytotoxic potential. This polyglutamated form of pemetrexed has a much greater affinity for TS than the parent compound. Because of this high affinity and long intracellular retention, pemetrexed may have greater clinical activity than other antifolates and TS inhibitors. Moreover, continued buildup of pemetrexed polyglutamates suppresses GARFT and inhibits purine synthesis. Readers are referred to a recent review by Adjei (2003) for a comprehensive analysis of the mechanism of action of pemetrexed and facts surrounding its preclinical and clinical development.

The antitumor activity of pemetrexed is dependent on the size of cellular folate cofactor pools; therefore, toxicity increases with folate deficiency. When folates are abundant, toxicity is diminished and efficacy is optimized. Thus, contrary to earlier fears about supplementation with folates, maintaining robust folate levels is critical to reducing toxicity and improving safety. Because of this finding in animal models, low doses of folic acid now are administered in clinical regimens to maintain adequate folate stores (Goldman & Zhao, 2002).

Antifolates traditionally have been associated with severe toxicities in some patients. In early clinical trials, half of all patients experienced grade 3 or 4 neutropenia. Grade 4 neutropenia with grade 3 or 4 infection, grade 3 or 4 diarrhea, or grade 3 or 4 mucositis was associated with potentially life-threatening and, in some cases, lethal complications.

During early phase II trials, homocysteine and methylmalonic acid, which are markers of vitamin deficiency, were collected before treatment (Niyikiza, Baker, et al., 2002; Niyikiza, Hanauske, et al., 2002). Subsequent analyses indicated that pretreatment total plasma homocysteine levels reliably predict severe thrombocytopenia and neutropenia with or without associated grade 3 or 4 diarrhea, mucositis, or infection. Similarly, pretreatment methylmalonic acid levels consistently and independently predicted grade 3 or 4 diarrhea and mucositis. Patients with elevated baseline levels of homocysteine or both homocysteine and methylmalonic acid had a high risk of severe toxicity. The results of these analyses set the stage for prospective clinical intervention to protect patients from pemetrexed-induced severe toxicity and possibly improve the drug’s efficacy (Niyikiza, Baker, et al.; Niyikiza, Hanauske, et al.).

**Phase I Studies**

In three phase I trials, pemetrexed was infused over 10 minutes; each study used different dosing schedules (Boyer, Rivory, & Clarke, 2002). Based on the occurrence of objective responses, convenience of administration, and ability to give repeated doses, a schedule of pemetrexed 500 mg/m² once every three weeks was used for phase II studies. Because pemetrexed can suppress bone marrow function, dose-limiting toxicities were neutropenia and thrombocytopenia. Significant mucositis, rash, and fatigue also occurred. Liver function test abnormalities were transient and without clinical sequelae (Boyer et al.).

**Phase II Single-Agent Study in Malignant Pleural Mesothelioma**

In a phase II multicenter trial of chemotherapy-naive patients with histologically proven MPM, single-agent pemetrexed demonstrated modest activity (14.1% response rate). Patients supplemented with folic acid and vitamin B₁₂ experienced less toxicity, received more treatment cycles, and had a five-month greater median overall survival than patients who received no supplementation (Scagliotti et al., 2003).

Patients received pemetrexed 500 mg/m² via IV over 10 minutes every three weeks. Initially, 21 patients received only pemetrexed. After a protocol change, 43 patients received vitamin supplementation consisting of 350–1,000 mcg oral folic acid beginning one to two weeks before the first dose of pemetrexed and throughout the study, as well as 1,000 mcg of vitamin B₁₂ given intramuscularly one to two weeks prior to the first dose of pemetrexed and administered about every nine weeks throughout the study. Dexamethasone 4 mg or an equivalent corticosteroid was given orally twice daily the day before, day of, and day after each pemetrexed dose to prevent or reduce severity of skin rash (Scagliotti et al., 2003).

No complete responses occurred, but partial responses were seen in 9 of 64 patients (14.1%). Seven of the nine responders had...
received vitamin supplementation. Median survival for all patients was 10.7 months. Median overall survival was 13.0 months for supplemented patients compared with 8.0 months for nonsupplemented patients. Patients who received vitamin supplements completed more cycles of therapy than did nonsupplemented patients (median = 6 versus 2 cycles) (Scagliotti et al., 2003).

Grade 3 or 4 neutropenia (23.4%) and grade 3 or 4 leukenia (18.8%) were the most common hematologic effects. The incidence of grade 3 or 4 neutropenia was 52.4% among nonsupplemented patients compared with 9.3% of those who received supplements. Fatigue and febrile neutropenia were the most commonly reported nonlaboratory events. The incidence usually was lower in the supplemented patients (Scagliotti et al., 2003).

**Combination Studies**

Because preclinical studies suggested additive or synergistic effects, pemetrexed was evaluated in combination with other anticancer agents. Two phase I trials combined pemetrexed and platinum analogs (Hughes et al., 2002; Thodtmann et al., 1999). In a study of pemetrexed and cisplatin, 5 of 11 patients (45%) with MPM had a partial response (Thodtmann et al.). At the maximum tolerated dose over all cycles of 600 mg/m² pemetrexed and 75 mg/m² cisplatin, 7 of 12 patients experienced grade 3 or 4 neutropenia and 8 patients experienced grade 3 or 4 anemia. Only one of three patients with grade 3 neutropenia or grade 4 anemia was treated at the recommended phase II pemetrexed dose of 500 mg/m² and cisplatin 75 mg/m².

In a trial combining pemetrexed and carboplatin at escalating dose levels in 27 chemotherapy-naive patients with MPM, 8 patients had a partial response (32%) (Hughes et al., 2002). Seventy percent of patients noticed an improvement in symptoms, usually after only two courses. Median time to progression was 305 days, and median survival was 451 days. The main toxicities were hematologic, particularly neutropenia, although they were short-lived and caused few clinical problems.

A multicenter, randomized, single-blind phase III study compared pemetrexed and cisplatin (226 patients) versus cisplatin alone (222 patients) in patients with MPM (Vogelzang et al., 2003). Three drug-related deaths (7%) were noted in 43 patients with MPM in the early stages of this clinical trial (43 patients were enrolled in the trial before vitamin supplementation was recognized as a way to reduce toxicity). Subsequently, folic acid and vitamin B₁₂ supplements were required for all patients receiving pemetrexed and for those subsequently enrolled in the study. As a result, three patient subgroups were defined by supplementation status: (1) never supplemented (NS) patients who completed treatment before the protocol change, (2) partially supplemented (PS) patients who began treatment before the protocol change, and (3) fully supplemented (FS) patients who began treatment after the protocol change.

The treatment regimen was similar to that of the single-agent study. Oral folic acid 350–1,000 mcg was administered one to two weeks prior to starting chemotherapy. Vitamin B₁₂ 1,000 mcg was administered intramuscularly every nine weeks starting one to two weeks prior to chemotherapy. Dexamethasone 4 mg was given twice daily the day before, day of, and day after pemetrexed to reduce the risk of severe skin rash.

Median survival time for patients treated with pemetrexed and cisplatin was 12.1 months versus 9.3 months for those receiving cisplatin alone. In the FS subgroup, median survival was 13.3 months for the combination therapy and 10 months for single therapy (p = 0.051). This difference was similar for the FS and FS/PS subgroups.

One-year survival rates for patients treated with pemetrexed and cisplatin were 50% versus 38% for the cisplatin-treated patients (p = 0.012). Rates for FS patients on pemetrexed and cisplatin were 56.5% versus 41.9%, respectively (p = 0.011). Rates were similar for FS/PS subgroups.

Median time to disease progression was 5.7 months for patients treated with pemetrexed and cisplatin compared with 3.9 months for cisplatin-treated patients (p = 0.001). This difference was similar for both the FS and FS/PS subgroups.

Patients receiving combination therapy plus vitamins experienced greater improvement in all efficacy parameters than those receiving the same regimen without vitamins. Supplementation also allowed patients to receive more cycles of treatment. Moreover, no adverse effects of vitamin supplementation on efficacy were reported. Response rates were 41.3% in the combination therapy arm and 16.7% in the control group (p < 0.001).

Severe toxicity was not common in the control arm. In the pemetrexed and cisplatin arm, the most common hematologic toxicities were grade 3 or 4 neutropenia (27.9%) and grade 3 or 4 leukenia (17.7%). Patients taking vitamin supplements had a notable reduction in hematologic toxicity, specifically grade 3 or 4 neutropenia and leukenia.

Table 1 shows toxicities for the FS group compared with PS/NS patients for combined FS/PS versus NS patients (Vogelzang et al., 2003). The incidence of grade 3 or 4 neutropenia was significantly higher among NS/PS patients (41.4%) compared with FS patients (23.3%) (p = 0.011). This difference was similar when PS/FS patients were compared with NS patients. A similar trend was observed for leukenia: FS/NS, 25.8% versus FS, 14.9% (p = 0.073). Overall improvement in severe toxicity has been observed in other pemetrexed studies since vitamin supplementation became an essential part of pemetrexed therapy.

In general, nonhematologic toxicities were infrequent, although the incidences of nausea, vomiting, fatigue, diarrhea, dehydration, and stomatitis were higher in the pemetrexed and cisplatin arm. In the pemetrexed and cisplatin arm, the FS subgroup experienced consistently less toxicity, except for dehydration, including less than a 1% incidence of febrile neutropenia.

Prior to vitamin supplementation, three drug-related deaths (7%) occurred among 43 patients. No treatment-related deaths occurred in the trial after vitamin supplementation was added. Fourteen patients died while on combination therapy or within 30 days of the last dose compared with eight patients who received cisplatin only. These deaths were considered to be disease related (Vogelzang et al., 2003). Alimta now is FDA-approved for the treatment of mesothelioma in combination with cisplatin.

**Interventions to Minimize Pemetrexed Toxicity**

In the phase III mesothelioma registration trial reviewed in the previous section (Vogelzang et al., 2003), less toxicity overall and a reduction in grade 3 or 4 hematologic and nonhematologic toxicities such as neutropenia, febrile neutropenia, and infection with grade 3 or 4 neutropenia were reported when folic acid and vitamin B₁₂ were administered before treatment. To reduce treatment-related toxicity, patients should be instructed to take a single, low-dose (350–1,000 mcg) oral folic acid supplement or a multivitamin containing folic acid on a daily basis. At least five single, daily doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed. Dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed (Eli Lilly and Company, 2003).

Patients also must receive one intramuscular injection of vitamin B₁₂ during the week preceding the first dose of pemetrexed and every three cycles thereafter. Subsequent vitamin B₁₂ injections may be given the same day as pemetrexed. In clinical trials, the dose of folic acid studied ranged...
from 350–1,000 mcg, and the dose of vitamin B12 was 1,000 mcg. The most commonly used dose of oral folic acid was 400 mcg (Eli Lilly and Company, 2003).

Skin rash has been reported in patients not pretreated with a corticosteroid. Pretreatment with dexamethasone or its equivalent reduces the incidence and severity of cutaneous reactions. In clinical trials, dexamethasone 4 mg the day before, day of, and day after pemetrexed administration (Nowak, Lake, Kindler, & Robinson, 2002).

**Laboratory Monitoring**

Before each pemetrexed dose, patients should undergo a complete blood cell count, including differential and platelet counts. Absolute neutrophil count (ANC) should be greater than or equal to 1,500 cells/mm³ and platelets greater than or equal to 100,000 cells/mm³ prior to scheduled administration of each cycle. Periodic blood chemistry tests should be collected to evaluate renal and hepatic function. Although pemetrexed is eliminated primarily unchanged when eliminated by the kidneys, clinical experience in patients with creatinine clearance below 45 ml/minute is limited. Therefore, patients whose creatinine clearance is less than 45 ml per minute should not receive pemetrexed (Eli Lilly and Company, 2003).

**Dose Reductions**

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Administration of pemetrexed may be delayed to allow sufficient time for recovery, at which time patients should be retreated according to dose-modification guidelines (Eli Lilly and Company, 2003) (see Tables 2–4).

For hematologic toxicities, 75% of the previous dose of both drugs should be administered when the nadir ANC is less than 500/mm³ and nadir platelets are greater than or equal to 50,000/mm³. When nadir platelets are less than or equal to 50,000/mm³ regardless of nadir ANC, reduce the dose of both drugs by 50% (see Table 2).

If patients develop nonhematologic toxicities, excluding neurotoxicity, greater than or equal to grade 3 (with the exception of grade 3 transaminase elevations), pemetrexed should be withheld until resolution to less than or equal to the patient’s pretreatment value. Treatment should be resumed according to the manufacturer’s guidelines (Eli Lilly and Company, 2003) (see Table 3). For any grade 3 or 4 toxicities, except mucositis and grade 3 transaminase elevations and any diarrhea requiring hospitalization, the dose of both drugs should be reduced to 75% of the previous dose. For grade 3 or 4 mucositis, 50% of the previous dose of pemetrexed and 100% of the cisplatin dose should be given.

In the event of neurotoxicity, the recommended dose adjustment for pemetrexed and cisplatin is as follows. If National Cancer Institute Common Toxicity Criteria grade is 2, only the dose of cisplatin should be reduced 50%. Patients should discontinue therapy if grade 3 or 4 neurotoxicity is observed (see Table 4). Pemetrexed therapy should be discontinued if a patient experiences any hematologic or nonhematologic grade 3 or 4 toxicity (except grade 3 transaminase elevations) after two dose reductions or immediately if grade 3 or 4 neurotoxicity is observed.

When treating older patients, no dose reductions other than those recommended for all patients are necessary. No indication has emerged from clinical trials that patients 65 years or older are at increased risk of adverse events compared with patients younger than 65 years.

Patients with creatinine clearance of at least 45 ml per minute required no dose adjustments in clinical trials, other than those recommended for all patients. Again, no patient whose creatinine clearance is less than 45 ml per minute should receive pemetrexed. Even though pemetrexed is not metabolized extensively by the liver, patients with hepatic impairment, such as bilirubin more than 1.5 times the upper limit of normal (ULN) or transaminase more than 3.0 times the ULN if hepatic metastasis is absent or more than 5.0 times the ULN if hepatic metastasis is present, have not been studied specifically (Eli Lilly and Company, 2003).

**Drug Interactions**

Concomitant administration of nephrotoxic drugs or substances that are eliminated as a result of glomerular filtration and tubular...
secretion could result in delayed clearance of pemetrexed. In vitro studies with human liver microsomes have suggested that pemetrexed would not cause clinically significant interactions with drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2 (Eli Lilly and Company, 2003).

Although ibuprofen 400 mg four times daily can be taken with pemetrexed in patients with normal renal function (creatinine clearance ≥ 80 ml/minute), caution should be exercised when giving ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance of 45–79 ml/minute). These patients should avoid taking nonsteroidal anti-inflammatory drugs (NSAIDs) with short elimination half-lives for two days before, the day of, and two days after administration of pemetrexed.

Because of the lack of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least five days before the day of, and two days after administration of pemetrexed.

TABLE 2. DOSE MODIFICATION FOR PEMETREXED AND CISPLATIN HEMATOLOGIC TOXICITIES

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadir absolute neutrophil count (ANC) &lt; 500/mm³ and nadir platelets &gt; 50,000/mm³</td>
<td>75% of previous dose (both drugs)</td>
</tr>
<tr>
<td>Nadir platelets &lt; 50,000/mm³ regardless of nadir ANC</td>
<td>50% of previous dose (both drugs)</td>
</tr>
</tbody>
</table>

Overdose

Reported symptoms of pemetrexed overdose include neutropenia, anemia, thrombocytopenia, mucositis, and rash. Anticipated complications of overdose include bone marrow suppression as manifested by neutropenia, thrombocytopenia, and anemia. In addition, infection with or without fever, diarrhea, and mucositis may be seen (Eli Lilly and Company, 2003).

No known antidote exists for pemetrexed overdose. If overdose occurs, general supportive measures should be instituted as deemed necessary by the attending physician. Management should include consideration of leucovorin or thymidine rescue.

Storing and Handling

Pemetrexed should be stored at controlled room temperature (i.e., 20°C–25°C or 68°F–77°F [US Pharmacopeia]). It is not light sensitive.

Pemetrexed should be administered 30 minutes prior to cisplatin. Standard cisplatin pre- and posthydration procedures should be followed. Preparation of pemetrexed for IV infusion is as follows (Eli Lilly and Company, 2003).

1. Use appropriate aseptic technique during the reconstitution and further dilution of pemetrexed for IV infusion administration.
2. Calculate the dose and the number of pemetrexed vials needed. Each vial contains 500 mg of pemetrexed and an excess of pemetrexed to facilitate delivery of label amount.
3. Prior to administration, reconstitute 500 mg vials with 20 ml of 0.9% sodium chloride injection (preservative free) to yield a solution containing 25 mg/ml pemetrexed. Gently swirl each vial until the powder is dissolved completely. Further dilution is required.
4. The appropriate volume of reconstituted pemetrexed solution should be diluted further to 100 ml with 0.9% sodium chloride injection (preservative free) and administered as an IV infusion over 10 minutes.
5. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
6. Because pemetrexed and the recommended diluent contain no antimicrobial preservatives, reconstituted and infusion solutions should be used immediately.

Chemical and physical stability of reconstituted and infusion solutions of pemetrexed was demonstrated for up to 24 hours after reconstitution of the original vial when stored at controlled room temperature. Pemetrexed is not a vesicant.

7. Discard any unused portion.

Discussion

MPM remains a devastating diagnosis for a patient. No known cure exists for this relatively rare cancer, and the prognosis is dismal. Progress has been slow, and therapeutic nihilism has pervaded this area of investigation for many decades. Ongoing research is focused on identifying active new drugs to improve treatment outcomes, and subtle but increasing optimism seems to accompany nascent discoveries. Novel approaches such as immune therapy, gene therapy, vaccines, and targeted cytostatic agents are being studied actively as a core group of focused investigators enthusiastically seeks to develop new therapies and improve patients’ lives (Nowak et al., 2002).

Clearly, much work remains to be done, but the emergence of pemetrexed as a viable new component of treatment for MPM represents a significant advance in a heretofore stagnant area of clinical research. Researchers are expected to continue to build on the success of this new combination, and new treatment strategies will increase hope for patients stricken with this unmerciful disease.

Implications for Nursing Practice

As previously discussed, during pemetrexed clinical development, markers of vitamin deficiency (homocysteine, methylmalonic acid, and cystathionine) were collected in an effort to identify patients at increased risk of severe toxicities. These efforts were based on preclinical observations with another antifolate, lometrexol, which suggested that dietary folic acid intake was associated

TABLE 3. DOSE MODIFICATION FOR PEMETREXED AND CISPLATIN NONHEMATOLOGIC TOXICITIES

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>Pemetrexed</th>
<th>CISPLATIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3 or 4 toxicities except mucositis</td>
<td>75% of previous dose</td>
<td>75% of previous dose</td>
</tr>
<tr>
<td>Any diarrhea requiring hospitalization</td>
<td>75% of previous dose</td>
<td>75% of previous dose</td>
</tr>
<tr>
<td>Grade 3 or 4 mucositis</td>
<td>50% of previous dose</td>
<td>100% of previous dose</td>
</tr>
</tbody>
</table>

1 National Cancer Institute Common Toxicity Criteria, excluding neurotoxicity

2 Except grade 3 transaminase

with efficacy and toxicity. Analysis of these markers showed a statistically significant increased risk of severe toxicity (including death) for patients with elevated homocysteine and methylmalonic acid. These markers are sensitive surrogates for functional folic acid and vitamin B12 status (Niyikiza, Baker, et al., 2002; Niyikiza, Hanauske, et al., 2002). In an attempt to prevent sporadic severe toxicity, all patients treated with pemetrexed in clinical trials were required to take dietary amounts of oral folic acid daily accompanied by intramuscular injections of vitamin B12 every nine weeks. This intervention effectively reduced homocysteine and methylmalonic acid levels and significantly reduced the incidence of severe toxicity.

Results from the phase III study of pemetrexed and cisplatin in MPM have verified that adding folic acid and vitamin B12 reduces toxicity without negatively affecting efficacy (Vogelzang et al., 2003). In fact, efficacy improved in the supplemented group of patients, as did the mean number of cycles administered.

For the reasons cited earlier, patients must be counseled on compliance with this intervention. In clinical trials, patients were administered pemetrexed if they had taken 5 doses of folic acid in the preceding 7 days or 10 doses in the preceding 14 days. One intramuscular injection of vitamin B12 was required before the first dose of pemetrexed was administered and then given about every nine weeks. Subsequent injections could be given on the same day as pemetrexed.

In summary, to realize the full benefit of adding pemetrexed to cisplatin, nurses must become knowledgeable about the preparation and administration of pemetrexed, including the necessity of supplementation with folic acid and vitamin B12. As with all drugs, careful attention must be paid to patient selection, laboratory monitoring, contraindications, and appropriate interventions in the event of adverse reactions or overdose. Much of this information has been reviewed herein, but practitioners are urged to consult and adhere to the guidelines published in the manufacturer’s prescribing information for pemetrexed (Eli Lilly and Company, 2003).

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References


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