Overview of Phase I/II Pemetrexed Studies

By Axel R. Hanauske, MD, PhD [2], Christian Dittrich, MD [3], and Jorge Otero, MD [4]

Pemetrexed (Alimta) is an antifolate that is effective in the inhibition of multiple enzyme targets including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. The compound has been evaluated in several phase I trials, both as single agent and in combination with other cytotoxic agents. The initial schedule selected for further investigation in phase II trials was pemetrexed 600 mg/m2 as a 10-minute infusion on day 1 every 21 days. During the subsequent phase II development, the dose of pemetrexed was adjusted to 500 mg/m2 due to bone marrow and gastrointestinal toxicities. The adjusted dose of pemetrexed was well tolerated throughout the late-phase drug development program. Preclinical evidence suggests that pemetrexed has additive or synergistic activity when combined with many other clinically important anticancer agents, including gemcitabine (Gemzar), fluorouracil, carboplatin (Paraplatin), oxaliplatin (Eloxatin), paclitaxel, and vinorelbine (Navelbine). Doselimiting toxicities in these studies were primarily hematologic, and there was no evidence of cumulative hematologic toxicity. During the drug development program it was discovered that supplementation with folic acid and vitamin B12 profoundly increased the tolerability of pemetrexed. The studies discussed in this review demonstrate that pemetrexed is well tolerated as a single agent and will be an important contribution to combination chemotherapy regimens.

Pemetrexed (Alimta) is a novel multitargeted antifolate antimetabolite that inhibits, among other enzymes, thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT). The primary targets of pemetrexed control pivotal steps in the de novo synthesis of pyrimidines and purines. The multitargeted nature of pemetrexed is confirmed by in vitro experiments demonstrating that both thymidine and hypoxanthine are required to prevent pemetrexed-induced cytotoxicity.[1] Three initial single-agent phase I studies were conducted to explore different treatment schedules of pemetrexed. These schedules comprised administration of the compound weekly * 4 every 6 weeks, daily for 5 days every 21 days, and once every 21 days. Pemetrexed was administered as a 10-mg/m2 intravenous (IV) infusion over 10 minutes. Phase I Trials of Single-Agent Pemetrexed

Rinaldi et al reported a single-agent phase I study with pemetrexed administered as a 10-minute infusion every week for 4 weeks. The treatment was repeated after 6 weeks in patients with advanced solid tumors.[2] A total of 25 patients received doses ranging from 10 to 40 mg/m2/wk. The doselimiting toxicity consisted of neutropenia that was completely reversible. Nonhematologic toxicities were mild, and no grade 3 or 4 nonhematologic toxicities were reported. The maximum tolerated dose was determined to be 40 mg/m2/wk and the recommended phase II dose utilizing this administration schedule was 30 mg/m2/wk. Two patients with advanced colorectal cancer experienced minor responses. Based on the results of this study, Rinaldi and colleagues conducted a second phase I trial.[3] In this study, pemetrexed was administered as IV infusion over 10 minutes every 21 days. A total of 37 patients with advanced solid tumors received doses ranging from 50 to 700 mg/m2. The maximum tolerated dose was found to be 600 mg/m2 and the recommended dose for subsequent phase II trials was determined to be 600 mg/m2. Neutropenia, thrombocytopenia, and cumulative fatigue were dose-limiting toxicities. Partial responses were noted in patients with advanced pancreatic cancer (n = 2) and advanced colorectal cancer (n = 2), with minor responses in patients with advanced colorectal cancer (n = 6). The third single-agent phase I trial with pemetrexed was conducted by McDonald and colleagues.[4] In this study, pemetrexed was administered as an IV infusion over 10 minutes daily for 5 days. The treatment was repeated every 21 days. Thirty-eight patients with advanced malignancies received pemetrexed with doses ranging from 0.2 to 5.2 mg/m2. The maximum tolerated dose was found to be 4 mg/m2, with neutropenia being the leading dose-limiting toxicity. One patient with metastatic non-small-cell lung cancer (NSCLC), one with metastatic colon cancer, and one with pancreatic cancer experienced minor responses. A comparison of the results from these three phase I studies indicated a relationship between the maximum tolerated dose treatment schedules; however, myelosuppression and epithelial toxicities as manifested by mucositis and/or diarrhea remained as predominant toxicities (Table 1). Additional nonhematologic toxicities included fatigue and rash. Because of the convenient administration schedule, the achievable dose intensity, and the extent of...
anecdotal antitumor activity observed, the every-21-day schedule was selected for further development of pemetrexed. The recommended phase II dose of 600 mg/m\(^2\) was subsequently reduced to 500 mg/m\(^2\) in order to further optimize the tolerability of pemetrexed and to prepare for early clinical trials with combination regimens. None of the single-agent phase I studies used supplementation of patients with folic acid and vitamin B\(_{12}\). The added value of vitamin supplementation to the safety of pemetrexed was only discovered after the agent had already entered its first registration phase III registration trial. Pharmacokinetic parameters of pemetrexed were evaluated in these phase I studies and yielded the following conclusions: at clinically used dose ranges, pemetrexed is eliminated from serum, with a mean terminal elimination half-life of 2 to 3 hours.[5] A linear relationship between area under the concentration-time curve (AUC) and dose was noted. Within 24 hours after administration of the compound, 70% to 90% of the administered dose is recovered in the urine. Hepatic metabolism of parent compound is minimal leading to negligible amounts of biologically inactive metabolites. There was no evidence for renal toxicities of pemetrexed in patients with normal creatinine clearance despite the fact that pemetrexed is renally eliminated. Nevertheless, in order to determine whether comedication with potentially nephrotoxic agents may lead to renal toxicities, a phase I trial was recently completed which evaluated the effects of combining ibuprofen with pemetrexed in patients with advanced cancer. Preliminary pharmacokinetic data indicated that coadministration of these two agents did not affect creatinine clearance or pharmacokinetic variables of pemetrexed.[6]

### Table 1

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Dose-Limiting Toxicities</th>
<th>Maximum Tolerated Dose</th>
<th>Vitamin Supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rinaldi et al[2]</td>
<td>Neutropenia</td>
<td>40 mg/m(^2)/wk</td>
<td>No</td>
</tr>
<tr>
<td>Rinaldi et al[3]</td>
<td>Neutropenia, thrombocytopenia, cumulative fatigue</td>
<td>600 mg/m(^2)</td>
<td>No</td>
</tr>
<tr>
<td>McDonald et al[4]</td>
<td>Neutropenia, reversible liver biochemistry</td>
<td>4 mg/m(^2)/wk</td>
<td>No</td>
</tr>
</tbody>
</table>

Pemetrexed underwent extensive evaluation in preclinical studies to determine if the agent could be combined with other clinically used cytotoxic agents, including platinums, gemcitabine (Gemzar), cyclophosphamide (Cytoxan), the taxanes, doxorubicin, vinorelbine (Navelbine), and radiation.[7] Findings of synergistic or additive antitumor effects in human tumor xenografts and cell lines suggested that these combinations warranted further evaluation in clinical trials. Table 2 summarizes clinical studies that have been conducted with pemetrexed combined with a variety of other clinically relevant compounds, and details will be presented below. These trials have demonstrated that pemetrexed is a versatile and well-tolerated drug that can be combined at full doses with all compounds studied, laying the basis for a broad subsequent drug development program. **Pemetrexed Combination With Gemcitabine**

The cytotoxicity and potential underlying mechanisms of the combination of pemetrexed and gemcitabine have been evaluated in several preclinical studies involving a variety of tumors and using simultaneous and sequential administration.[8-14] Data have shown that the combination results in synergistic cytotoxicity when administered sequentially but antagonism with concurrent administration. Optimal synergy was observed with the pemetrexed \(\rightarrow\) gemcitabine sequence in studies of HT29 colon carcinoma xenografts[8] and MIA PaCA-2, PANC-1, and Capan-1 pancreatic cancer cell lines.[9] In contrast, the highest level of synergy in a study of colon adenocarcinoma cell lines LoVo, WiDR, and LRWZ occurred when gemcitabine administration preceded that of pemetrexed, while the reverse sequence resulted in additive and synergistic effects.[10] In the latter trial, an increase in TS expression, which is associated with resistance to conventional antifolates, was noted in all cell lines. Experiments in HT29 colon cancer cells evaluated the cell-cycle-modulating effects of pemetrexed by flow cytometry as a potential mechanism to increase gemcitabine potency.[8] A decrease in HT29 proliferation rate correlated with an accumulation of cells in S phase after 12 to 24 hours of pemetrexed exposure. The authors concluded that
synchronization of HT29 cells by pemetrexed was effecting a change in the nucleotide pools by inhibition of target enzymes- TS, GARFT, and DHFR- that in turn potentiated cytotoxicity of exposure to gemcitabine. Other studies have also shown S-phase cell synchronization after pemetrexed treatment.[9,10]

In MIA PaCa-2, PANC-1, and Capan-1 pancreatic cell lines, Giovannetti et al demonstrated that pemetrexed treatment significantly enhanced gene expression and activity of deoxycytidine kinase (dCK), a key enzyme involved in pyrimidine salvage pathways and in the rate-limiting step in gemcitabine activation.[9] Rauchwerger et al studied the role of the equilibrative-sensitive nucleoside transporter (es-NT) in gemcitabine sensitivity.[11] Cellular uptake of gemcitabine requires transport across the plasma membrane by sodiumindependent (equilibrative) mechanisms (es-NT), the activity of which is a prerequisite for tumor growth inhibition by gemcitabine.[12] Thus, combining a nucleoside analog with agents that increase NT expression, such as TS inhibitors, would theoretically increase the potential for cell kill through depleting the nucleotide pool.[13,14] In experiments carried out using TS inhibitors (5-FU and raltitrexed [Tomudex]) with gemcitabine administered concurrently and sequentially in three human pancreatic and one human bladder cancer cell lines, TS inhibitor pretreatment significantly augmented cell kill relative to singleagent gemcitabine and significantly increased cell surface es-NT content over basal levels in two of the pancreatic cancer cell lines. Results were maximal when TS inhibitor treatment preceded gemcitabine administration.[11] Thus, potential mechanisms of synergy with the pemetrexed → gemcitabine sequence include TS inhibition, depletion of nucleotide pools, S-phase synchronization of cells, and activation of es-NT and dCK. Mechanisms for additive or synergistic effects observed with the reverse sequence are less clear as yet. Based on the demonstration of preclinical cytotoxic synergy, a phase I trial of
pemetrexed in combination with gemcitabine was conducted in 56 patients with advanced solid
tumors who had received at least one previous chemotherapy regimen.[15] Adjei et al used
sequential administration of gemcitabine followed by pemetrexed, based on their in vitro clonogenic
assays demonstrating cytotoxic synergy in cultured human colon carcinoma cells with this sequence
but not the reverse sequence.[15] Patients in group I (n = 35) received gemcitabine at 1,000 or
1,250 mg/m² IV over 30 minutes on days 1 and 8, and pemetrexed on day 1 only, 90 minutes after
gemcitabine, at escalating doses ranging from 200 to 600 mg/m² given IV over 10 minutes. Courses
were repeated every 3 weeks. Because 57% of courses were associated with neutropenia that
required reduction/omission of the day 8 gemcitabine dose, group II patients (n = 21) received the
pemetrexed on day 8 instead of day 1. Neutropenia was the principal dose-limiting hematologic
toxicity in both groups I and II and seemed to be dose related; no infections were noted in patients
with severe neutropenia. The median neutrophil count nadir was on day 7 in group I and day 14 in
group II patients, indicating a relationship between the nadir and pemetrexed administration. The
maximum tolerated dose for group I was determined to be gemcitabine at 1,000 mg/ m² and
pemetrexed at 500 mg/m² due to prolonged (> 5 days) grade 4 neutropenia in four of six patients
receiving the 1,250-mg/m² gemcitabine dose. For group II, the maximum tolerated dose was
gemcitabine 1,250 mg/m² and pemetrexed 500 mg/m² due to life-threatening neutropenia seen at the higher pemetrexed dose of 600 mg/m². The primary nonhematologic toxicity
was elevated hepatic transaminase level in 71% of treatment courses, most cases of which were
mild to moderate and rapidly reversible. Other toxicities included nausea, fatigue, and rash. Patients
receiving pemetrexed on day 8 (group II) had fewer and less severe toxicities and fewer dosage
interruptions than those receiving pemetrexed on day 1 (group I). Among 55 assessable patients,
objective responses were confirmed in 7 of 34 group I and 6 of 21 group II patients with tumors,
including colorectal cancer (n = 3), non-small-cell lung cancer (n = 3), cholangiocarcinoma (n = 2),
ovarian cancer (n = 2), mesothelioma (n = 1), breast cancer (n = 1), and adenocarcinoma of
unknown primary site (n = 1). Twelve of these patients had partial responses and one was
considered a mixed response, with response durations of at least 3 months. An additional 27
patients had stable disease, with durations of stable disease ranging from 1 to 11 cycles after the
initial evaluation at cycle 2. Pharmacologic evaluations conducted in four group I patients at the
maximum tolerated dose showed no alteration of pemetrexed pharmacokinetics based on
gemcitabine pretreatment, although the sample size was small. Recommended dose and schedule of
this regimen for phase II study was gemcitabine 1,250 mg/m² on days 1 and 8 with pemetrexed 500
mg/m² given 90 minutes after gemcitabine on day 8, every 21 days.[15] Phase II studies of the
pemetrexed/ gemcitabine combination are being carried out in advanced-stage non- small-cell lung,
breast, and pancreatic cancer, as described elsewhere in this supplement. **Pemetrexed and
Cisplatin**

In a phase I study of pemetrexed and cisplatin, two administration schedules were investigated
based on the hypothesis that because pemetrexed is primarily eliminated by renal excretion,
hydration required for cisplatin administration may potentially modulate the clearance of
pemetrexed and thus impact on antitumor activity or toxicity.[16] In order to investigate this
hypothesis in a clinical setting, one patient cohort (n = 40) received pemetrexed followed by
hydration and cisplatin on day 1 of a 21-day cycle. Another cohort (n = 11) was treated with
pemetrexed on day 1 without any hydration, followed by hydration and cisplatin on day 2 of a 21-day
cycle. In both cohorts, pemetrexed was administered as an IV infusion over 10 minutes.
The maximum tolerated dose for both schedules was pemetrexed 600 mg/m$^2$ and cisplatin 100 mg/m$^2$, demonstrating that both compounds can be combined at fully active clinical doses. Dose-limiting toxicities consisted mainly of myelosuppression. Ten patients in cohort 1 experienced partial responses, and one patient with head and neck cancer had a complete response. In the second cohort, two patients experienced partial responses. Most notably, five of 11 patients with pleural mesothelioma developed confirmed and independently validated partial responses, indicating a profound antitumor effect of this combination in malignant pleural mesothelioma—a disease for which at that time no established treatment was available. Antitumor responses were also noted in other tumor types including NSCLC, colorectal cancer, melanoma, and cancer of unknown primary. The recommended doses for subsequent clinical studies were determined to be pemetrexed 500 mg/m$^2$ and cisplatin 75 mg/m$^2$ with administration of both agents on day 1. Based on the provocative results of this study, pleural mesothelioma was chosen as the primary target tumor entity for approval, and additional studies, including a single-agent phase II trial and a phase I trial with pemetrexed and carboplatin, were initiated. A courageous step was taken by initiating the ultimately successful pivotal phase III registration trial based on the results of the phase I combination trial of pemetrexed and cisplatin.

Pemetrexed in Combination With Carboplatin

The combination of pemetrexed and carboplatin was evaluated in a phase I trial conducted by Hughes and colleagues.[17] Twenty-seven patients with MPM received escalating doses of pemetrexed (400 mg/m$^2$ to 500 mg/m$^2$) and carboplatin (AUC 4 to 6). Pemetrexed was administered as a 10-minute infusion and carboplatin was administered as a 30-minute infusion, both on day 1 every 21 days. Pemetrexed at 500 mg/m$^2$ and carboplatin at AUC 6 was the maximum tolerated dose; three of five patients at this dose level experienced grade 4 neutropenia as the dose-limiting toxicity. Nonhematologic toxicities at the maximum tolerated dose included nausea, vomiting, and stomatitis. There were no grade 4 nonhematologic toxicities reported at this dose level. Two courses at all dose levels were complicated by grade 3 elevation of transaminase levels. Response to therapy was a secondary outcome and was measured in all patients. Of the 25 patients evaluable for response, there were eight confirmed partial responses, for an overall response rate of 32%. Five of the eight patients who experienced partial responses had stage IV disease, and five patients had mesothelioma of epithelial histology. All of the patients who received treatment with pemetrexed and carboplatin experienced cancer-related symptoms at the start of chemotherapy. Nineteen (70%) of the original 27 patients accrued experienced relief in cancer-related symptoms while on study. Median overall survival was 451 days and median time to disease progression was 405 days. Figure 1 shows the response of a patient on this study. The recommended phase II dose for this combination was determined to be pemetrexed 500 mg/m$^2$ and carboplatin AUC 5, which allowed for administration of full doses of both agents. Pemetrexed in Combination With Oxaliplatin

The combination of pemetrexed and oxaliplatin was evaluated in a dose-escalating phase I clinical trial in patients with metastatic solid tumors.[18] Forty-five patients received pemetrexed at 300 to 500 mg/m$^2$ followed by oxaliplatin (as a 2-hour infusion) at 85 to 130 mg/m$^2$ given on day 1, every 21 days. Only 5 of 16 patients experienced dose-limiting toxicities at the highest dose level, pemetrexed 500 mg/m$^2$ and oxaliplatin 130 mg/m$^2$; therefore, the maximum tolerated dose was not
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Pemetrexed in Combination With Vinorelbine

A dose-escalating phase I study was conducted in patients with advanced or metastatic cancer.[19] Vinorelbine was given on days 1 and 8, with pemetrexed administered on day 1 of a 21-day cycle. Vitamin supplementation was initiated at dose level 3. The majority of patients had received prior chemotherapy and all patients had a performance status of 0 or 1. Partial responses were noted in three patients. The maximum tolerated dose was pemetrexed 700 mg/m² and vinorelbine 30 mg/m², where the dose-limiting toxicity-grade 3 fatigue—was reported in two patients. One patient died of cardiac arrest that was not considered to be treatment related. The recommended phase II doses of this combination regimen were pemetrexed 600 mg/m² on day 1 and vinorelbine 30 mg/m² on days 1 and 8.[19]

Phase I Studies of Pemetrexed Combination Regimens in Breast Cancer

In a phase I study, Hughes and colleagues[20] combined pemetrexed with doxorubicin in 26 patients with advanced cancer. The dose of doxorubicin ranged from 40 to 60 mg/m² and pemetrexed was administered at doses ranging from 400 to 500 mg/m². Treatment cycles were repeated every 21 days. The maximum tolerated dose was reached at a dosage of pemetrexed 500 mg/m² combined with doxorubicin 50 mg/m². Both patients enrolled at that dose level experienced dose-limiting toxicities—hematologic and gastrointestinal. The doses recommended for subsequent phase II trials were pemetrexed 500 mg/m² and doxorubicin 50 mg/m². No objective responses were noted; however, seven patients achieved stable disease after six courses of therapy. The authors recommended, based on the documented activity of both pemetrexed and doxorubicin, that this combination be studied in patients with breast cancer. Paridaens and coworkers[21] reported a phase I combination trial of pemetrexed and epirubicin (Ellence) in patients with locally advanced or metastatic breast cancer (n = 22) using pemetrexed 400 to 500 mg/m² and epirubicin 60 to 80 mg/m². (The study patients, including 15 chemo naive patients had not received prior chemotherapy, and completed a median of five cycles.) The maximum tolerated dose was reached at a dosage of pemetrexed 500 mg/m² and epirubicin 80 mg/m². Dose-limiting toxicities consisted of neutropenia grade 4 and febrile neutropenia. At the time these data were reported, seven patients had a partial response, two had an unconfirmed partial response, and five had stable disease with mature follow-up. Although the maximum tolerated dose was reached at dose level 3 above, accrual at pemetrexed 600 mg/m² and epirubicin 75 mg/m² continued to determine the best recommended phase II regimen. A final analysis with mature data is pending.

Pemetrexed in Combination With Cyclophosphamide

A tumor-type-restricted phase I study of pemetrexed and cyclophosphamide in patients with metastatic breast cancer was based on promising in vitro and preclinical in vivo observations.[22] Pemetrexed was administered over 10 minutes on day 1 of a 21-day cycle as an IV infusion followed by cyclophosphamide administered over 30 minutes as an IV infusion approximately 20 minutes after the start of the pemetrexed infusion. Dexamethasone (4 mg twice daily, days 0, 1, 2) was administered prophylactically to prevent rash. Folic acid and vitamin B₁₂ were supplemented in order to minimize pemetrexed-induced hematologic and nonhematologic toxicities. Three to six patients were treated at each dose level. At an interim analysis, 38 patients had been entered into the trial. The median age was 55 years (range: 32-81 years) and their performance status was 0 (n = 26, 68%), 1 (n = 10, 26%), or 2 (n = 2, 5%). Prior chemotherapy was administered as neoadjuvant (n = 7), adjuvant (n = 20), first-line metastatic (n = 4), second-line metastatic (n = 12), or thirdline metastatic (n = 11) therapy, with some of the patients having received chemotherapy in more than one treatment setting. A total of 231 cycles of chemotherapy were administered with a median of four cycles (range: 1-23 cycles) per patient. At the interim evaluation, the dose level reached was 1,100 mg/m² of pemetrexed in combination with cyclophosphamide 600 mg/m². The latter had been escalated up to 800 mg/m² in combination with pemetrexed 600 mg/m². Dose-limiting toxicities occurred at various dose levels and included febrile neutropenia, grade 4 neutropenia, grade 4 AST.
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Based on the in vitro observation that pemetrexed is a very potent radiation sensitizer, the combination of pemetrexed and concurrent radiotherapy was investigated in a phase I study conducted by Vokes and colleagues.[26,27] Pemetrexed was administered on day 1, every 21 days for two cycles with concurrent radiotherapy. Radiation was delivered at 2 Gy daily 5 days a week for a total dose of 40 to 66 Gy. Eighteen patients with NSCLC (n = 15) and esophageal carcinoma (n = 3) were enrolled. Patients could have received prior chemotherapy to be eligible for the study. The protocol was amended to include the administration of carboplatin at AUC 4, following pemetrexed administration. Preliminary data by Mauceri et al indicate that single-agent pemetrexed can be combined with radiation and that subsequent development of this compound also in a radiochemotherapy setting is warranted.[26] One patient experienced a dose-limiting toxicity consisting of grade 3 neutropenia with infection was reported at the pemetrexed 500-mg/m² dose level. Grade 3 or 4 hematologic toxicities consisted of grade 3 neutropenia in three patients and grade 3 hypokalemia in one; nonhematologic toxicities consisted of grade 3 dysphagia in one patient. Among 16 evaluable patients, five had a partial response, five additional patients had stable disease, and six patients showed a progression of their disease. The authors concluded that pemetrexed can be safely combined with radiation therapy at doses of up to 600 mg/m² with no increase of infield toxicities. Because platinum-containing doublets combined with radiation therapy represent standard regimens in the first-line treatment of NSCLC, the protocol of this trial has been amended to include carboplatin-based regimens. The trial will subsequently enroll chemotherapy-naïve patients with advanced NSCLC who will receive pemetrexed 500 mg/m² every 21 days for two cycles, carboplatin at AUC 4 mg/mL/min on days 1 and 22 following pemetrexed, and radiation therapy at 2 Gy five times per week for a total dose up to 40 to 66 Gy. Vitamin Supplementation

After it became evident that supplementation with folic acid and vitamin B12 led to improved tolerability of pemetrexed, questions regarding the optimal vitamin dose and increasing the dose of pemetrexed in light of the improved safety profile arose. In response to this, Hammond and colleagues designed a phase I study in patients with advanced cancer.[28] The primary objective was to determine the maximum tolerated dose and secondary objectives were to evaluate toxicity and safety and antitumor activity, to perform a pharmacokinetic analysis, and to determine recommended phase II doses. Patients were randomly assigned to receive escalating doses of pemetrexed with "standard-dose" vitamins (folic acid 350 to 1,000 µg orally per day) or "high-dose" folic acid (HDFA, 5 mg orally per day starting 2 days before administration of pemetrexed and lasting until day 3). Patients receiving HDFA were further divided into two groups based on the extent of their previous therapy. "Heavily" pretreated patients were defined as having received > 2 courses of mitomycin, > 6 courses of an alkylating agent, > 4 courses of carboplatin, or previous radiotherapy. Two of six heavily pretreated patients experienced dose-limiting toxicities at the pemetrexed 925-mg/m² dose level (grade 3 transaminase elevation, grade 4 febrile neutropenia). In these patients, the maximum tolerated dose of pemetrexed with standard-dose vitamins and HDFA was 800 mg/m². The available data suggest that standard-dose vitamins or HDFA allow further dose escalation of pemetrexed; however, future studies will be needed to demonstrate whether this potential for dose increase will also result in an actual increase in therapeutic benefit, response, and survival, or not.[28] Selected Phase II Studies

Currently, five single agent phase II studies of pemetrexed have been performed in patients with advanced breast cancer.[29-33] Antitumor activity was documented both in untreated and heavily (> 2 prior regimens for metastatic disease) pretreated patients In a study conducted by Miles and colleagues,[29] five chemotherapy-naïve patients were treated with pemetrexed as first-line therapy and an additional 16 patients had been pretreated with adjuvant chemotherapy and received pemetrexed as first-line therapy for metastatic disease. The objective response rate was 28% with a median response duration of 8.0 months. However, not surprisingly, a subsequent trial demonstrated that heavily pretreated patients who had previously received anthracyclines and taxanes as well as capecitabine showed a lower response rate of 10% and a median response duration of 5.9 months.[30] Phase II studies of pemetrexed-based combinations are either completed or in progress, and include combinations with doxorubicin, epirubicin, paclitaxel, docetaxel, vinorelbine, oxaliplatin, carboplatin, gemcitabine, and cyclophosphamide. Other articles in this supplement cover these data.
Conclusion
Pemetrexed is a novel antifolate antimetabolite with marked singleagent and combination therapy activity in a variety of cancers, including thoracic and breast cancers. The primary toxicities seen in these studies were bone marrow suppression, mucositis, diarrhea, and skin reaction. Supplementation with folic acid and vitamin B₁₂ profoundly reduced the frequency of grade 3 and 4 toxicities and further improved the tolerability of this agent. Pemetrexed can be safely combined with a large variety of clinically relevant antitumor agents and thus lends itself as an optimal partner for combination regimens. Dose-limiting toxicities of pemetrexed in these combinations remain myelosuppression, transaminase elevations, and epithelial side effects as demonstrated by either mucositis and/or diarrhea. While there is no evidence for any organ-specific cumulative toxicities of pemetrexed, longer-lasting treatments with this agent may be accompanied by fatigue. However, this rarely constitutes a reason to discontinue therapy.

Disclosures: Dr. Hanauske has acted as a consultant for Eli Lilly.

References:


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