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FDA Drug Approval Summaries: Pemetrexed (Alimta®)

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Explain the mechanism of action of a recently approved new cancer drug, pemetrexed.
2. Describe the adverse-event profile of pemetrexed and a novel approach for toxicity reduction.
3. Discuss the rationale for the FDA approval of pemetrexed.

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Abstract

The purpose of this report is to summarize information on pemetrexed (LY231514; MTA; Alimta®; Eli Lilly and Company; Indianapolis, IN), a drug recently approved by the U.S. Food and Drug Administration (FDA). The review of the efficacy and safety of pemetrexed is summarized below. Pemetrexed is a pyrrolopyrimidine antifolate. It inhibits thymidylate synthase, glycinamide ribonucleotide formyltransferase, and dihydrofolate reductase. In a single, randomized, single-blind, multicenter phase III trial, the efficacy and safety of pemetrexed combined with cisplatin (Platinol®; Bristol-Myers Squibb; Princeton, NJ) were compared with those of single-agent cisplatin in 448 patients with malignant pleural mesothelioma. Two hundred twenty-six patients were randomized to receive pemetrexed and cisplatin, while 222 patients were randomized to receive cisplatin alone. The primary study end point was survival. Median survival times were 12.1 months for the pemetrexed plus cisplatin treated arm and 9.3 months for the cisplatin alone arm. Pemetrexed causes myelosuppression. The most common adverse events were neutropenia, fatigue, leukopenia, nausea, dyspnea, and vomiting.

On February 4, 2004, pemetrexed was approved by the FDA in combination with cisplatin for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery. The recommended dose of pemetrexed is 500 mg/m^2 administered as an i.v. infusion over 10 minutes on day 1 of each 21-day cycle together with cisplatin at a dose of 75 mg/m^2 infused over 2 hours beginning 30 minutes after the pemetrexed infusion. Patients must receive oral folic acid and vitamin B_{12} injections prior to the start of therapy and continue these during therapy to reduce severe toxicities. Patients should also receive corticosteroids with chemotherapy to reduce the risk of skin rashes. Approval was based on superior survival as a clinical benefit.

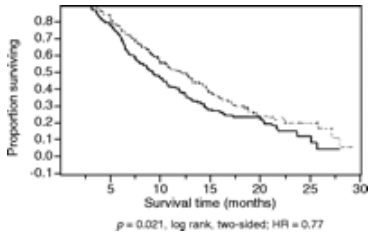
Pemetrexed Alimta® Malignant pleural mesothelioma

INTRODUCTION

Malignant mesotheliomas arise primarily from the surface serosal cells of the pleural, peritoneal, and pericardial cavities and are highly aggressive neoplasms. The etiology of malignant mesothelioma is primarily exposure to asbestos fibers [1]. Simian virus 40 has also been implicated in the etiology [2]. Malignant pleural mesothelioma (MPM) most typically develops 20–50 or more years after the first documented asbestos exposure, commonly in the fifth to seventh decade of life. With median survival durations of 10–17 months from onset of symptoms and 9–13 months from diagnosis, the prognosis is poor for patients with these neoplasms.

Although the Cancer Committee of the College of American Pathologists provides a protocol for the examination of specimens from patients with MPMs, histological diagnosis remains difficult [3]. Earlier staging systems were not uniform, and the International Mesothelioma Interest Group Staging System (IMIG) updated several earlier staging systems after taking into consideration information about the impact of tumor (T) and nodal (N) status on survival [4]. Evaluations with two series of patients validated the staging system [5, 6].

Surgical resection of MPM is possible in only a minority of patients. Fewer than 15% of these patients live beyond 5 years [6, 7]. Curative radiotherapy, although available, is limited by the tumor volume to be treated and by toxicities to surrounding normal tissue [8]. Chemotherapy with single agents, such as doxorubicin (Adriamycin®; Bedford Laboratories; Bedford, OH), methotrexate with rescue, 5-azacytadine, 5-fluorouracil,



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Safety

The primary safety analysis was done on the fully vitamin-supplemented subgroup, which consisted of 168 patients on the pemetrexed plus cisplatin arm and 163 on the cisplatin alone arm.

Neutropenia (24.4%), fatigue (17.3%), leukopenia (15.5%), nausea (11.9%), dyspnea (11.3%), and vomiting (10.7%) were the most commonly reported grade 3 and 4 adverse events (Table 3⇓). Febrile neutropenia and neutropenic sepsis were relatively infrequent. The incidences of grade 3 and 4 anemia and thrombocytopenia were 6% and 5.4%, respectively, in patients on the pemetrexed plus cisplatin arm (Table 4⇓). The most common clinical cause of dose delay in both arms was neutropenia, followed by reduced creatinine clearance, leukopenia, anemia, stomatitis, and infection. Cycle 4 was the cycle of therapy with the most clinical delays in both treatment arms.

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Table 3.

Common adverse events (>10% of patients) in fully vitamin-supplemented patients

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Table 4.

Adverse events in fully supplemented patients

Toxicities were higher in the pemetrexed plus cisplatin arm than in the cisplatin alone arm. Severe toxicities were reduced with the use of folic acid and vitamin B_{12} supplementation.

DISCUSSION

In a single, randomized, single-blind trial, the combination of pemetrexed and cisplatin, compared with cisplatin alone, showed a statistically significant longer overall survival in MPM patients. Pemetrexed plus cisplatin is the first treatment for MPM to demonstrate a survival benefit. The trial was changed while ongoing, and supplementation with folic acid and vitamin B_{12} was added.

Although a single trial, a large number of independent investigators from multiple international centers contributed data to the trial, and there was a substantial increment in survival of 3 months. The efficacy of pemetrexed was supported by an improvement in pulmonary function tests.

Survival analyses in all intent-to-treat patients and in the randomized and treated patients both favored the pemetrexed plus cisplatin group at a statistically significant level. Survival analyses in the fully vitamin-supplemented subgroup and in the subgroup with a confirmed histologic diagnosis of MPM also favored the pemetrexed plus cisplatin group at a borderline statistical significance level.

Similar to the approved label of pemetrexed, numerical values for response rate are not mentioned in the body of this article. As anticipated prior to the study, there was considerable discrepancy in tumor response evaluations among the study investigators, the study independent reviewers, and the FDA reviewers. The FDA review of the submitted images could confirm tumor response in only 47 of the 94 patients in the pemetrexed plus cisplatin treatment group for whom the applicant claimed a tumor response. Although tumor response rate appeared higher in the pemetrexed plus cisplatin treatment group, the exact numbers are very uncertain.

Following therapy with pemetrexed, toxicities appeared to be higher in patients with elevated pretherapy homocysteine levels. Elevated baseline homocysteine levels (≥10 μmol/l) highly correlated with severe hematological and nonhematological toxicities. Thus, every patient since December 1999 treated in the trial with pemetrexed was supplemented with folic acid and vitamin B_{12} to improve patient safety.

In patients treated with the combination therapy with full vitamin supplementation, the common adverse events were neutropenia, fatigue, leukopenia, nausea, vomiting, and dyspnea. In comparison with the nonsupplemented subgroup of patients, toxicities were reduced by folate and vitamin B_{12} supplementation. Despite supplementation, the combination of pemetrexed and cisplatin produces a high degree of toxicity.