Malignant Pleural Mesothelioma (MPM) continues to be a challenging problem; because few patients may be treated with radical surgery and conventional chemotherapy have achieved very dismal results. Pemetrexed is a new drug with multitarget antifolate activity which seems to be particularly active in many solid tumors and also in MPM. The principal clinical experiences of pemetrexed alone or in combination with other compounds, chiefly platinum and its derivative, are reported. The Italian study on 1114 cases of MPM treated over 30 months is discussed and the definitive results will be available after a complete external review of all responsive patients.

Key words: pemetrexed, malignant pleural mesothelioma, chemotherapy

Introduction

Malignant Pleural Mesothelioma (MPM) is an aggressive tumor that arises from the surface serosal cells of pleural cavities, and it is primarily associated with the exposure to Chrysolite, a particular asbestos fiber. Individuals who have been exposed for long periods of time during their work the highest risk; the projected lifetime risk among these workers, when exposed from early adulthood, is as high as 20%.

It has been estimated that in UK the annual deaths for MPM will raise until approximately 2010 [1]; in Italy the incidence and mortality for MPM are dramatically increased from the period between 1978–1982 and 1993–1998: in fact, the respective figures for male and female population describing epidemiological data raised from 0.9 and 0.4 to 2 and 0.9 × 100 000 of incidence, and from 0.89 and 0.39 to 1.89 and 0.85 × 100 000 of the mortality [2].

MPM commonly develops in the fifth to seventh decade of age, typically 20 to 50 years after the first documented asbestos exposure. Prognosis is poor with a median survival of 10 to 17 months from symptoms onset and 9 to 13 months from diagnosis. Until recently, chemotherapy has not changed the natural history of the disease, and radiotherapy has a minimal impact on survival and in symptom palliation [3]. The role of surgery is uncertain for the most part of patients, chiefly as consequence of the delayed diagnosis, although a small number of cases have shown a long-term survival after radical surgery [4].

In recent years, a large body of knowledge has been acquired from basic research on MPM; in more than 70% of mesotheliomas a hyper-expression of EGFR, independently from histotype, has been demonstrated; moreover, the presence of SV40, a monkey oncogenic virus, in the non-epithelial mesothelioma seems to correlate with increased production of Vascular Endothelial Growth Factor and poor prognosis [5]. Further data are available about the Cyclo-Oxygenase 2 hyper-expression as a result of the chronic inflammatory process due to the exposure to asbestos, and the peculiar characteristic of the presence, in the MPM cells, of Reduced Folate Carrier; both these biological aspects could be a good target for novel therapeutic approaches [6, 7].

Pemetrexed (Alimta®) is a novel antimetabolite that inhibits the folate-dependent enzymes thymidylate synthase, dihydrofolate reductase, and glycaminide ribonucleotide formyltransferase. Pemetrexed has demonstrated activity in clinical trials in a large variety of tumor types, including lung, breast, colon, pleura, pancreas, stomach, bladder, head and neck, and cervix. Pemetrexed is rapidly metabolized into active polyglutamate forms which are potent inhibitors of several tetrahydrofolate cofactor-requiring enzymes critical for the synthesis of purines and thymidin. Functionally, pemetrexed acts as a prodrug for its polyglutamate forms. Two different transporters are known to take extracellular folates, and some antifolates, into the cell: these are the reduced folate carrier and the folate receptor. One of the characteristics that make pemetrexed unique is that a focused approach has been developed to eliminate and control some clinical toxicities. Multivariate analyses demonstrated that pre-treatment total plasma homocysteine levels significantly predicted severe thrombocytopenia and neutropenia, with or without associated grade 3/4 diarrhea, mucositis, or infection. Routine vitamin B12 and folic acid supplementation have resulted in decreased frequency/severity of toxicities associated with pemetrexed without affecting efficacy, making this novel antifolate a safe and efficacious anticancer agent [8].

The ‘social’ characteristic of the disease and the expected increasing incidence in the next few years, together with the availability of more effective therapies make the MPM one of the most interesting fields of basic and clinical research in oncology today.

Clinical experiences

Pemetrexed, as single agent, has been used in a multicenter cooperative phase II study carried out in 64 patients chemotherapy-naive with measurable disease at the dose of...
500 mg/m² every 3 weeks; the most part of patients (43) received vitamin supplementation to control the hematological severe toxicity. Nine (14.1%) of the patients achieved a partial remission, and the median estimated overall survival was 10.7 months. The addition of folinic acid and vitamin B₁₂ represented a great progress, because the dramatic reduction of hematological toxicity was reinforced by an increased efficacy: 7 of the nine partial responders received vitamin supplementation, and the median overall survival was 13 months for supplemented versus 8 months for patients not given vitamins. The authors concluded that pemetrexed as single agent, and with vitamin supplementation, is a safe and potentially useful therapeutic option for MPM [9].

The most important study on pemetrexed and MPM is the prospective, randomized, phase III trial published by Vogelzang [10] in which 226 patients were randomized to receive pemetrexed and cisplatin on a three-week schedule and 222 patients as a control group received cisplatin as single agent. Median survival time in the pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the control arm \( P = 0.020, 2\)-sided log-rank test). The hazard ratio for death of patients in the pemetrexed/cisplatin arm versus those in the control arm was 0.77. Median time to progression was significantly longer in the pemetrexed/cisplatin arm: 5.7 months versus 3.9 months \( P = 0.001, \). Response rates were 43.3% in the pemetrexed/cisplatin arm versus 16.7% in the control arm \( P < 0.001 \). After the first 117 patients vitamin supplementation was given to the patients and a dramatic fall in the incidence of severe haematological and gastrointestinal side effects were observed. Although the design and conduction of the study deserve some critical aspects, however the authors conclude that, despite some limitation in the design and conduction of the study, pemetrexed in combination with cisplatin should be a safe and effective treatment for patients with MPM. This study represents a further step in the therapy of mesothelioma and currently the combination of pemetrexed and cisplatin is considered, the standard treatment for MPM [11].

After this experience further studies have been presented, chiefly in abstract form, employing the combinations of cisplatin/carboplatin or gemcitabine and pemetrexed. A non-randomized, open-label study was designed to gather additional efficacy and safety data of pemetrexed alone or in combination with cisplatin. Treatment in chemo-naïve patients consisted of pemetrexed 500 mg/m² in combination with cisplatin 75 mg/m² given once every 21 days for a maximum of 6 cycles. All patients received folic acid, vitamin B₁₂, and steroid prophylaxis. Antitumor response from 295 patients shows 10 patients (3.4%) with CR, 42 (14.2%) with PR, 129 (43.7%) with SD and 114 (38.6%) with PD. The number and severity of serious adverse events were acceptable and predominantly related to cisplatin toxicities. On the basis of the favourable toxicity profile and the promising response rate, the combination of pemetrexed and cisplatin should be a new standard treatment for MPM [12].

Three phase II studies have been presented at the ASCO meeting in 2005; two with the combination of pemetrexed and platinum compounds and the last with the combination of pemetrexed and gemcitabine. In the Orlando’s study, 73 all patients were accrued in an expanded access program designed to give pemetrexed as single agent to patients relapsed after previous treatments, or combination of pemetrexed plus cisplatin to 80 naïve patients. Response rates were 5.5% for pemetrexed alone and 32.5% for the combination treatment; in 41.1% and 36.3% respectively patients were in stable disease, and the median survivals were 4.1 and 7.6 months [13]. The Italian study, by Ceresoli et al., used pemetrexed and carboplatin AUC 5 given both on day 1 every 3 weeks to 78 consecutive naïve patients. The response rate was 20% and stable disease was achieved in 44% of patients; the median time to progression was 6 months [14]. In each study the toxicity was limited because all of the patients being treated with vitamin supplementation. The combination of pemetrexed and gemcitabine is of particular interest chiefly for unfit patients with severe co-morbidities unable to receive platinum compounds. Two schedules have been investigated: in each group of patients pemetrexed was given at 500 mg/m² on day 1 every 21 days; in the first group, 56 patients received pemetrexed on day 8 and gemcitabine 1250 mg/m² on days 1 and 8; in the second group, 52 patients received the same drugs, same doses, but pemetrexed was given on day 1. The authors concluded that pemetrexed plus gemcitabine is active in MPM and has an acceptable toxicity profile. Administering pemetrexed on D8 is associated with a higher response rate although the median TTP is similar in both cohorts [15].

In conclusion, it seems currently reasonable to consider pemetrexed a real progress in the treatment of MPM, especially in combination with cisplatin or carboplatin.

The primary objective of this study is to provide the drug for the treatment of patients with MPM. Patient access to pemetrexed has been given to this protocol prior to and during its review by Regulatory Agencies for commercial release. The secondary objectives include: (i) improving safety knowledge, (ii) determining the time to progressive on, and (iii) determining the best overall tumour response. No restrictive criteria have been stated for the patients’ accrual: in particular naïve and previously treated patients have been registered. Each investigator had three therapeutic options: (A) pemetrexed 500 mg/m² i.v. over 10 min followed 30 min later by cisplatin 75 mg/m² i.v. over 2 h on day 1 of each 21-day cycle, (B)

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<th>Characteristics</th>
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<td>Evaluable patients</td>
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<tr>
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<td>Patients responsive (CR+PR)</td>
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<td>Pemetrexed alone</td>
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<td>Pemetrexed + Cisplatin or Carboplatin</td>
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pemetrexed 500 mg/m² i.v. over 10 min on day 1 of each 21-day cycle, or (C) pemetrexed 500 mg/m² i.v. over 10 min followed 30 min later by carboplatin AUC 5 i.v. over 30 min on day 1 of each 21-day cycle. Vitamin supplementation was administered to all patients according to the previously defined doses and schedules.

All patients were required to have the following characteristics to be enrolled in the study: histologically proven diagnosis of mesothelioma in patients not candidates for curative surgery; measurable or evaluable lesions; a minimum of 2 weeks from pleurodesis, PS Karnofsky ≥70; adequate organ function; personal compliance and geographic proximity, signed informed consent.

During a period of 30 months, from 12/02 to 05/05, 1114 patients have been enrolled in this study, from 84 Italian Oncology and Pneumology Clinical Centres. A preliminary analysis has been made on 322 evaluable patients whose principal characteristics are reported in Table 1.

No conclusive results are available and an independent review board will evaluate all patients who achieved CR, PR or stable disease; considering that this patient population is not selected, as for registrative clinical trials, and this series is consistent with the characteristics of patients daily admitted to the oncology and pneumology units. The preliminary feeling is that in terms of response rate, including stable disease, and in terms of toxicity, the use of pemetrexed, alone or in combination with platinum compounds, provides to the patients a good chance of therapy with a low profile of hematological and gastrointestinal toxicities. Definitive results of this large study will be available at the end of external review.

disclosures
Dr Marangolo has indicated that he is a member of the speakers’ bureau of Eli Lily Italia.

references