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A phase II trial of second-line pemetrexed in adults with advanced/metastatic osteosarcoma ☆

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Abstract *Background:* Osteosarcoma is the most common primary malignant tumour in young adults. An effective treatment strategy for relapsed patients is still not defined. Pemetrexed is a multitargeted antifolate with a mode of action similar to, and a range of action broader than that of methotrexate. The primary objective of this phase II study was to determine tumour response rate in patients with high-grade, advanced/metastatic osteosarcoma. Secondary endpoints included progression-free survival (PFS), overall survival (OS) and safety.

Methods: Pemetrexed 500 mg/m^2 was administered on day 1 of 21-day cycles with folic acid and vitamin B_{12} supplementation. At least 5 tumour responses in a targeted population of 32 were required to consider further investigation.

Results: Thirty-two patients (median age, 43.3 years; range, 18.6–76.0) with 1 prior chemotherapy regimen for high-grade advanced/metastatic osteosarcoma were enrolled. Thirty (93.8%) patients had an ECOG performance status $\leqslant$1 and 29 (90.6%) had metastases in the lung. One patient had partial response (3.1%) and 5 (15.6%) had stable disease. Median PFS and OS were 1.4 months (95% CI: 1.4–1.7) and 5.5 months (95% CI: 2.3–10.5), respectively. The most common drug-related grade 3/4 toxicities were leukopaenia, asthaenia and elevated alanine aminotransferase in 3 (9.4%) patients each. One patient died due to multi-organ failure considered possibly related to the study drug.

Conclusions: Pemetrexed 500 mg/m^2 administered on day 1 of 21-day cycles as second-line treatment to patients with advanced/metastatic high-grade osteosarcoma was generally well tolerated but did not meet minimal response expectations for further investigation in this patient population.

1. Introduction

Osteosarcoma is the most frequent primary cancer of bone (incidence: 0.03–0.2 per 100,000 per year).[1] At

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presentation, only 20–25% of patients have radiologically detectable metastases; however, almost all patients with high-grade osteosarcoma have micrometastases.[2] Treatment of osteosarcoma requires complex multimodality therapy (surgery with pre- and post-chemotherapy). The most active chemotherapeutic agents in the treatment of osteosarcoma are high-dose methotrexate, doxorubicin, cisplatin and ifosfamide.[2,3] The long-term survival rate of newly diagnosed patients with high-grade osteosarcoma without detectable metastasis has improved considerably compared with that of surgery alone (>60% versus 10–20%).[1]

The value of second-line chemotherapy and the best treatment strategy for relapsed patients with high-grade, advanced or metastatic disease are not well defined.[1] This is further confounded by the fact that few studies exist about the management of patients with relapsed osteosarcoma due to the relative rarity of the disease.[1] Consequently, outcomes to second-line treatment, such as tumour response rate, are not well established. Thus, metastatic osteosarcoma remains difficult to treat, with a lack of consensus regarding the choice of second-line therapy, and as such, new agents are continuously being evaluated for efficacy.

Pemetrexed, a multitargeted antifolate, is approved for use in combination with cisplatin for unresectable mesothelioma,[4] as a single agent for second-line as well as maintenance treatment of non-squamous advanced/metastatic non-small cell lung cancer (NSCLC),[5,6] and in combination with cisplatin for first-line treatment of advanced/metastatic non-squamous NSCLC.[7] Its primary mechanism of action is the potent inhibition of the folate-dependent enzyme thymidylate synthase[8,9]; dihydrofolate reductase and glycinamide ribonucleotide formyl transferase are secondary targets.[9] Pemetrexed has demonstrated broad-spectrum activity in various solid tumours and has a broader spectrum of action than its anti-folate predecessor, methotrexate, by virtue of its multitargeted capability and its ability to interfere with pyrimidine and purine synthesis. Given the wider range of action of pemetrexed compared with methotrexate, we decided to conduct this phase II trial evaluating pemetrexed treatment in patients with relapsed osteosarcoma to address this unmet medical need.

The primary objective of our phase II study of second-line pemetrexed therapy in patients with high-grade, advanced or metastatic osteosarcoma was to assess tumour response rate. Secondary objectives included measurements of progression-free survival (PFS), overall survival (OS) and safety.

2. Materials and methods

2.1. Eligibility criteria

Patients were eligible to participate in the study if they were $\geqslant$18 years of age, with an estimated life expectancy of at least 12 weeks and a histologically documented diagnosis of high-grade locally advanced or metastatic osteosarcoma that was not amenable to surgery, radiation or combined modality therapy with curative intent. Patients must have received one prior chemotherapy regimen for advanced disease; neoadjuvant and adjuvant chemotherapies were not counted towards this requirement. Pemetrexed was considered as second-line chemotherapy for advanced/metastatic disease. Prior radiation therapy was allowed to <25% of the bone marrow and must have been completed at least 4 weeks before study enrolment with complete recovery from acute toxic effects. Patients were required to have $\geqslant$1 unidimensionally measurable lesion (at least one measurable lesion outside the field of any prior radiation therapy) that met the Response Evaluation Criteria in Solid Tumours (RECIST)[10]; a performance status (PS) of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale and adequate haematologic (absolute neutrophil [segmented and bands] count [ANC] $\geqslant 1.0 \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L [in case of bone marrow disease: $\geqslant 75 \times 10^9$/L] and haemoglobin $\geqslant$9.0 g/dL), renal (calculated creatinine clearance [CrCl] $\geqslant$45 mL/min based on the standard Cockcroft and Gault formula), cardiac and hepatic functions.

Patients were excluded from the study if they had a serious concomitant systemic disorder (eg, active infection); a serious cardiac condition, such as myocardial infarction within 6 months of enrolment, angina or heart disease (New York Heart Association Class III or IV); a prior malignancy other than osteosarcoma, carcinoma in situ of the cervix or non-melanoma skin cancer unless treated $\geqslant$5 years before enrolment with no evidence of recurrence; central nervous system metastases unless the patient completed successful local therapy for this disease and had not been receiving corticosteroids for $\leqslant$4 weeks before enrolment; the presence of clinically detectable (by physical exam) third-space fluid retention; and the inability to discontinue aspirin, other non-steroidal anti-inflammatory agents or corticosteroids.

All patients provided written informed consent before study participation. The study was approved by the appropriate ethical review boards and conducted according to all applicable laws and regulations, good clinical practices and the ethical principles of the Declaration of Helsinki.

2.2. Study design and treatment plan

In this phase II, open-label, multicentre, single-arm study, pemetrexed was supplied by Eli Lilly and Company (Indianapolis, IN) at a dose of 500 mg/m^2 by a 10-minute intravenous infusion on day 1 of 21-day cycles. All patients received oral folic acid and vitamin B_{12} supplementation per the pemetrexed label.[11] In addi-