Efficacy of a combination of pemetrexed and multiple redo-surgery in an 11-year-old girl with a recurrent multifocal abdominal mesothelioma

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We report the case of an 11-year-old girl with a recurrent progressive locally advanced abdominal mesothelioma. First, there was an incomplete surgical resection without any complementary chemotherapy, followed by a slow progression of the disease. Three years later, after two macroscopically complete surgical resections of peritoneal and ovarian tumors, she failed to respond to treatment with gemcitabin–carboplatin and gemcitabin–cisplatin, and developed splenic tumors and large multicystic hepatic tumors. She was then treated with pemetrexed. The schedule of chemotherapy was pemetrexed 400 mg intravenously plus cisplatin 60 mg once every 3 weeks associated with folic acid and vitamin B12. The tumor reduction was evaluated with positron emission tomography scan and tomodensitometry every three courses. Chemotherapy tolerance was good apart from a grade III neutropenia at the second course, a fever of unknown origin at the fifth course and a grade III thrombocytopenia at the sixth course. As tolerance and clinical responses were good, pemetrexed posology was increased up to 10%. After six courses, hepatic and splenic lesion tumors were initially diminished and then stablilized. Thus, a surgical resection was attempted: a first surgery followed by a second one 3 days later allowed completion of a difficult left hepatectomy, and resection of the hilum and splenic tumors. Fourteen months after the surgery, the girl remained in partial remission with stable disease. So far, pemetrexed associated with cisplatin revealed a good tolerance and promising results regarding its antitumoral efficacy in a progressive metastatic abdominal mesothelioma in childhood. ***Anti-Cancer Drugs*** **17:1231–1234 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Malignant mesothelioma is an aggressive tumor that originates from serosal surfaces, such as the pleura or the peritoneum [1,2]. A majority of cases occur in the pleura, followed by the peritoneum, pericardium and tunica vaginalis testis [3]. Most mesotheliomas are associated with asbestos, although some are related to radiation or to virus SV40. This last hypothesis is controversial [4]. Background incidence for pleural mesothelioma is estimated to be around 1–2 cases per 1 000 000 inhabitants per year [5]. A French study reveals that annual incidence rates of peritoneal mesotheliomas are much lower [6]. Peritoneal mesothelioma represents approximately one-fifth to one-third of all forms of mesothelioma [7–9] and median survival ranges from 7 to 13.5 months [10]. Although mesothelioma's incidence is increasing, peritoneal mesothelioma is a very rare cancer in adults and pediatric cases are even rarer [1,11,12].

Adult patients with peritoneal mesothelioma can be palliated with systemic or intraperitoneal chemotherapies. Responsive chemotherapeutic agents are alkylating agents (cisplatin [13,14] or carboplatin [15], mitomycin C [16,17]), intercalating agents (doxorubicin [18,19]) or antimicrotubule agents (paclitaxel associated with cisplatin [20]). Antimetabolites can also be used: gemcitabine activity in malignant mesothelioma has been confirmed in phase II studies [21,22]. Available data also suggest that better results can be obtained by combining this agent with cisplatin [23]. In February and September 2004, the Food and Drug Administration (FDA) [24] and the European Medicines Agency [25], respectively, approved another antimetabolite, i.e. pemetrexed, for the treatment of malignant pleural mesothelioma in combination with cisplatin in adults when the disease is unresectable or when patients are not candidates for surgery. This new drug is an anti-folate that disrupts folate-dependent metabolic processes, essential for cell replication. To lower the risks of hematologic side-effects (the major ones with hepatic side-effects), it is necessary to take folic acid and vitamin B12 before, during and after treatment [26]. Janne *et al.* [27] showed a favorable safety profile and an acceptable disease

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control rate in adults with pemetrexed, irrespective of associated or not with cisplatin.

So far, pemetrexed administration has never been reported in children and mesothelioma treatment, and no standard treatment has been approved for this very rare disease either in adults [28,29] or in children.

Case report

An 8-year-old girl was complaining about abdominal pains and nausea. She felt weak, and lost appetite and weight. Imaging work-up suggested peritoneal mesothelioma, which was confirmed by laparoscopic biopsy. Surgical resection of numerous diffuse peritoneal and pelvic nodules, and an omentectomy was performed on 13 July 2001. No additional treatment was administered and a slow multifocal progression of the disease was observed. In March 2004, the girl presented multifocal macrocystic abdominal recurrence. A surgical resection of pelvic tumors was achieved on 11 March 2004, and a resection of right diaphragmatic and of segment IV hepatic tumors was achieved on 4 April 2004. Two months after the surgery, recurrence was, however, again detected as huge cystic tumors involving the entire left lobe, segment VIII and hilum of the liver, compressing the retrohepatic vena cava, along with para splenic lesions. A chemotherapy with gemcitabin 800 mg intravenously with carboplatin 250 mg intravenously was then initiated. After three courses, the lack of efficacy led us to replace carboplatin by cisplatin 60 mg. As gemcitabine tolerance was good, the posology was increased from 800 to 1600 mg. After a 5-month Gemzar (Eli Lilly, Indianapolis, Indiana, USA) administration, the tumor was still progressing; therefore, a new chemotherapy with pemetrexed (Almita; Eli Lilly) was decided. Pemetrexed was not used as first-line chemotherapy owing to the lack of data regarding its use in children and the lack of phase I trials that would have determined the adequate dosing.

The schedule of administration was the one recommended by the FDA [24]: pemetrexed (500 mg/m^2 intravenous, 400 mg as a 10-min intravenous infusion) and cisplatin (60 mg as a 2-h intravenous infusion) were given on day 1 of a 21-day cycle, associated with vitamin B12 intramuscularly and folic acid supplementation. The first course was initiated on 2 November 2004. During treatment, no major toxicity was registered. At the second course, the girl presented transitory anorexia and a grade III neutropenia. A tomodensitometry showed a 20 and 26% reduction size of two left-side liver tumors and disappearance of the segment VIII lesion. The positron emission tomography scan showed stable splenic lesions. As tolerance and clinical response were good after the third course, pemetrexed posology was increased up to 10% (450 mg) for the next three courses.

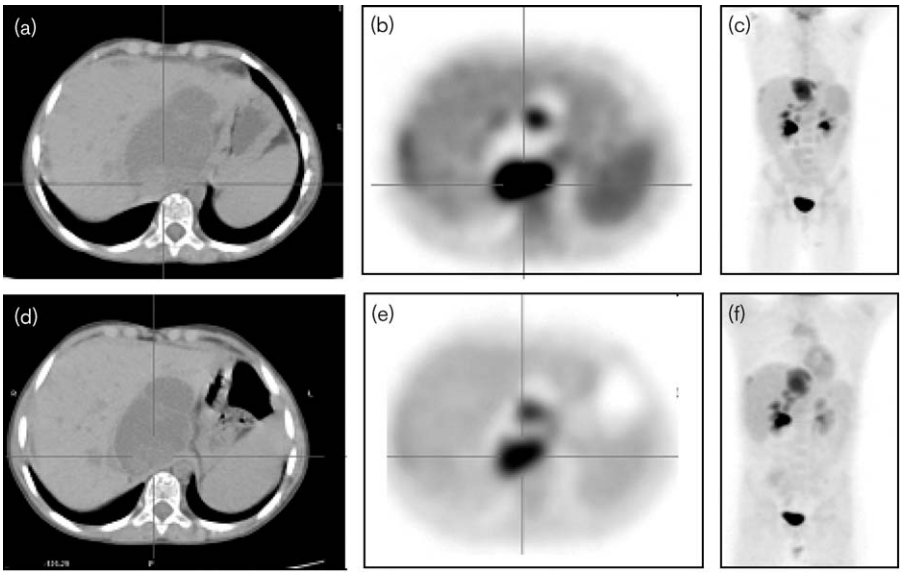
No serious toxicity was observed. At the fifth course, fever of unknown origin was treated with a probabilistic antibiotic therapy. At the sixth course, the girl had a grade III thrombocytopenia. After six courses, the liver lesions had a 35 and 50% tumor size reduction (Fig. 1).

Regarding the partial response obtained after these six courses, a pluri disciplinary decision of surgical resection was attempted in order to eradicate the lesions completely or, at least, to obtain a microscopic residual tumor. After informed consent of the family on the major risks of the procedure, a left hepatectomy was performed on 22 March 2005. A right branch to segment IV arising from the left hepatic artery had to be severed. As this procedure was well tolerated and liver function was not impaired, redo-surgery was performed 3 days later on 25 March 2005: the hilum tumor was resected, the splenic tumor enucleated and a cholecystectomy was performed. Post-operatively, the child developed acute hepatic failure (prothrombine time: 15%; alanine amino transferase: 2820 IU/l) related to thrombosis of the right hepatic artery, leading to multivisceral failure, liver abscesses and severe cholestasis (bilirubin: 515 µmol/l). Her status gradually improved and she was discharged from hospital 4 months after the surgery. Nevertheless, regarding the liver post-surgery impairment, additional chemotherapy and radiotherapy, initially considered to complete surgical resection, were cancelled. Fifteen months later, the young girl is alive with stable residual disease.

Discussion

Peritoneal mesothelioma is not clearly associated with one etiology or with specific risk factors. Our reported case is an 11-year-old girl who correlates with other case reports relating a higher disease frequency in girls [30] without obvious correlation with asbestos or radiations [31]. No standard treatment strategy is available owing to the rarity of this tumor, which is even rarer in young children. The first chemotherapy we administered in this young patient was gemcitabine associated to carboplatin, then to cisplatin, because of the reported efficacy in this pathology in adults [21–23]. Furthermore, gemcitabine produced encouraging results in a phase I pediatric trial in solid tumors [32]. The lack of efficacy led us to consider pemetrexed administration (Almita). Indeed, the efficacy of pemetrexed has been reported in recent studies on treatment of adult peritoneal mesothelioma [27,29]. Peritoneal mesothelioma is an uncommon cancer, even rarer in children, which is resistant to conventional therapy and results in short survival time. Therefore, this young girl was administrated pemetrexed at adult posology (500 mg/m^2) with the same folic acid and vitamin B12 prophylaxis. The child's tolerance was good and it therefore led us to increase slightly the pemetrexed posology. Six pemetrexed courses resulted in partial regression of tumors that authorized us to consider

Fig. 1



Evolution of liver lesion after pemetrexed courses. Upper panels: the beginning of pemetrexed chemotherapy. (a) Transverse image from tomodensitometry (TDM) shows a heterogeneous signal within the liver mass. (b and c) Images from [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography scan show dense areas of uptake within the mass. Lower panel: the end of pemetrexed chemotherapy. (d) Transverse image from TDM shows a smaller signal within the liver mass. (e and f) Images from FDG positron emission tomography scan show areas of decreased uptake.

redo-surgery. We decided to use this drug in the child because Janne *et al.* [27] reported a pemetrexed favorable safety profile (associated or not with cisplatin) and an acceptable disease control rate.

We report the first pediatric use of pemetrexed in an 11-year-old girl with a multifocal recurrent abdominal mesothelioma. Posology was similar to the adults as recommended by the FDA or European Medicines Agency and the toxicity was acceptable. Pemetrexed associated to cisplatin had noticeable efficacy in a highly progressive peritoneal mesothelioma. Five years after the initial diagnosis, and 14 months after pemetrexed use and tumor resection, the child is in partial remission with stable disease. This combination showed efficacy in the often fatal neoplasm in which the median survival time is less than 1 year [33].

Additional studies or reported cases are required to determine pemetrexed's concrete efficacy and toxicity.

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