Maintenance chemotherapy with pemetrexed in patients with malignant pleural mesothelioma – case series and review of the literature

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ABSTRACT

Malignant pleural mesothelioma is a rare neoplasm with poor prognosis. Surgical complete resection, which is the only radical therapy available, is only possible in a minority of patients who suffer from a locally advanced disease. Radiotherapy can be considered as an adjuvant therapy after surgery or as supportive treatment in palliative care. Attempts are also made at combining it with chemotherapy. In cases of locally advanced, non-resectable or metastatic disease, chemotherapy remains the treatment of choice. The most effective palliative chemotherapy is the pemetrexed plus cisplatin regimen.

We describe 3 cases of patients who underwent standard palliative chemotherapy with pemetrexed and cisplatin, manifesting good radiological and clinical response, followed by maintenance therapy with pemetrexed. The use of pemetrexed maintenance therapy helped achieve many years of disease control with acceptable toxicity. The consecutive stages of therapy were continuously discussed with our patients, and their informed consent was obtained. Pemetrexed maintenance therapy is not a standard procedure, but recent findings suggest it may be an efficacious option to consider in selected groups of patients. Further randomized prospective studies are needed, but a limiting factor is the rarity of the disease.

KEY WORDS: pemetrexed, pleural mesothelioma, maintenance therapy

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INTRODUCTION

Pleural mesothelioma is a rare disease with poor prognosis. It accounts for 0.1–0.2% of annual morbidities in Poland, and a similar rate of deaths. It affects males twice as often as females. In 2005 in Poland, 5-year survival did not exceed 18% in female patients and 8% in male patients [1]. Surgery offers radical treatment. Patients with advanced disease, whose general condition is good, are qualified for palliative chemotherapy (CHTH) involving cisplatin (DDP) and pemetrexed (PMT). They usually receive up to 6 cycles of chemotherapy, depending on their tolerance, and are subsequently followed up on for disease progression. No standard second-line treatment has yet been established. Several drugs are routinely used, but there is no scientific evidence as to their superiority over placebo or best supportive care (BSC). We describe cases of 3 patients, treated with the standard first-line chemotherapy regimen of PMT + DDP, in whom disease progression was not reported, and who were subsequently treated with maintenance pemetrexed. In all of them, there was long-term response to the treatment offered, with acceptable toxicity. As standard procedure, vitamin B_{12} was administered to the patients every 9 weeks, folic acid was administered daily, and dexamethasone was administered one day before the cytostatic agent, on the day of the cytostatic administration, and on the following day. To assess the response to treatment, modified RECIST (Response Evaluation Criteria in Solid Tumors) criteria were applied [2].

The first patient initiated palliative chemotherapy in June 2007, and continued treatment, with a break of a dozen or so months, until June 2014, when disease progression was confirmed by CT in accordance with the RECIST criteria. The second patient received systemic treatment from December 2008 to December 2014 (72 months). The therapy was discontinued due to an exacerbation of the patient's chronic kidney disease, having achieved complete radiological remission. The third patient initiated chemotherapy in November 2012 and continues treatment (June 2016), i.e. he has been in treatment for 43 months now.

In the first patient diabetes developed during treatment, most probably steroid-induced, and requiring insulin use. In the second patient renal insufficiency (CTCAE v4 grade 1) [3] was observed, which is why treatment had to be discontinued. There have been no significant complications in the third patient to date.

CASE DESCRIPTIONS

Case 1st

A 50-year-old male patient had previously been treated for arterial hypertension and stable coronary heart disease. In 2005, he suffered from pulmonary embolism, diagnosed based on the results of perfusion scintigraphy. Since 2005, recurrent fluid in the right pleural cavity had been reported in the patient. In November 2006, right-sided thoracotomy was performed. The collected material was too fine, though, to enable diagnosis. However, presence of neoplastic cells was confirmed, impossible to differentiate unequivocally in the pleural fluid. The immunohistochemistry findings did not rule out lung cancer or well-differentiated pleural mesothelioma. In March 2007, right-sided thoracotomy was repeated, with wedge resection of a fragment of the lower lobe, and collection of specimens from the parietal pleura. Based on the histopathology findings, *mesothelioma malignum pleurae* was diagnosed. Mucus staining was negative. The immunohistochemical reactions were as follows: mesothelium (+), calretinin (+), CEA (-), TTF-1 (-), Ber-Ep4 (-), EMA (+, membrane reaction).

The patient was qualified for surgical treatment in two stages. Initially, mediastinoscopy was performed, with specimens collected from the 4L, 4R and station 7 lymph nodes. As cancer cells were detected in station 4R lymph nodes, the planned second stage of treatment was aborted. The advancement of the disease made radical resection impossible, and so in June 2007, the patient was started on palliative chemotherapy involving cisplatin and pemetrexed. He received 6 chemotherapy cycles, during which his renal parameters worsened, followed by monotherapy with PMT, continued until June 2009, with partial remission (in accordance with the RECIST criteria) confirmed by CT. In October 2010, CT revealed progressive disease (PD) in the form of a thickened infiltration of the right pleura, reaching the thickness of 10 mm (earlier 5–6 mm). Infiltration of the intercostal muscles was suspected along the right posterior axillary line. Starting from November 2010, the patient was back on PMT. The consecutive follow-up CT examinations reported gradual increase in the measurable lesions, and in June 2014, the RECIST disease progression criteria were met. The patient required insulin treatment due to diabetes, most likely induced by steroids. His creatinine level was slightly elevated to 1.3 mg/dl (N < 1.2 mg/dl). Otherwise, the patient did not present any clinical complaints.

Case 2nd

A 57-year-old male with arterial hypertension, controlled with two different antihypertensives, was hospitalized in April 2007 for pneumonia and fluid in the right pleural cavity. CT was performed, followed by ultrasound-guided right-sided pleurocentesis, collecting 1500 ml of fluid with no cancer cells in it. Bronchofiberoscopy revealed signs of external compression on the basal segments of the right lower lung lobe. In October 2008, diagnos-

tics of the recurrent fluid in the right pleural cavity was continued, revealing cells of a non-small-cell cancer in the fluid. The histopathological picture of the pleural biopsy specimen was indicative of mesothelial hyperplasia with signs of reactive dysplasia. Fragments of pleura infiltrated by *mesothelioma malignum epithelioides* were detected. Computed tomography performed in October 2008 revealed an irregular solid infiltrative 103 × 55 mm lesion of the mediastinal pleura, visible on the border of the middle and lower right lobe. It was accompanied by hypodense oval-shaped infiltrations with marginal contrast enhancement, possibly corresponding with an 85 mm nodular infiltration, located along the right diaphragm crus. The lesion was adjacent to the pericardium and oesophagus. The lower right lung lobe was compressed, with atelectatic lesions. In segments 3, 4, and 5 of the right lung, there were micronodular interstitial lesions (ground glass opacities), indicative of cancer dissemination. Due to the extent of the lesions, the patient was disqualified from surgical treatment. Upon the initiation of chemotherapy, in December 2008, the patient's condition was very good, with ECOG performance status of 0, and lab test results within normal range. By April 2009, the patient received 6 cycles of chemotherapy (PMT + DDP), with worsening renal function (creatinine – 1.3–1.4 mg/dl, eGFR – 60 ml/min/1.73 m^2, N < 1.2 mg/dl). Computed tomography performed in April 2009 revealed partial remission, and decision was taken together with the patient to continue treatment with pemetrexed as monotherapy. In December 2014, the patient had to discontinue PMT chemotherapy due to the ever worsening renal function (creatinine – 2.1mg/dl, eGFR – 34 ml/min/1.73 m^2, CTCAE grade 1) as well as the slightly elevated levels of AST and ALT (< 2 × GGN, CTCAE grade 1). Due to the elevated creatinine level, pemetrexed was administered to the patient every 4 weeks in the last year of treatment. A follow-up CT performed in February 2015 revealed complete remission of the disease (CR). PD was reported in July the same year.

Case 3rd

A 63-year-old patient underwent a diagnostic process from August through October 2012 for dyspnoea and presence of fluid in the right pleural cavity. A CT test revealed numerous soft tissue nodules, 4 to 10 mm in size, connected at their bases, in the parietal pleura of the left lung and of the interlobar fissures as well as under the parietal pleura. Additionally, the test revealed the presence of fluid within the pleural cavity. Moreover, a polycyclic infiltrative 90 × 40 mm lesion was revealed in the anterior-inferior mediastinum, in the right cardiac-diaphragmatic angle, adjacent to the pericardial sac and pleura. The lesion was connected with a 48 × 19 mm infiltration, adjacent to the 6th rib in the parasternal segment, and several lymph nodes up to 12 mm in size. Bronchoscopy was performed, revealing a normal picture of the bronchi. Cytology of the fluid collected from the right pleural cavity failed to reveal the presence of neoplastic cells. In September 2012, right-sided videothoracoscopy was performed with drainage and talc pleurodesis. The initial histopathological interpretation of the parietal pleura specimens was *carcinomatosis pleurae*/*adenocarcinoma papillare*. Eventually, however, microscopic findings and the immunohistochemical profile led to the diagnosis of *mesothelioma malignum*: TTF1 (+/-), CDX2 (-), CK7(-), CK19(+), CK20(-), calretinin (+), WT-1 (+). A later CT examination, performed in October 2012, revealed a 57 × 37 mm infiltrative lesion in the right pulmonary hilus, nodules up to 18 mm in size, and a 63 mm layer of fluid in the right pleural cavity. Numerous lymph nodes were revealed in the mediastinum (up to 10 mm in diameter), and under the carina (up to 18 mm). There was a 55 × 50 mm infiltration over the right dome of the diaphragm, adjacent to the heart. A 6 mm hypodense focus was revealed in hepatic segment II, suspected of being a metastatic lesion. The patient was disqualified from radical surgical treatment.

When qualified for palliative chemotherapy, the patient's general condition was good, with an ECOG performance status of 0, with arterial hypertension controlled with two antihypertensives, and bilateral perceptive hypoacusis. No absolute contraindications were found to administer the DDP + PMT chemotherapy regimen. Lab test results revealed no abnormalities. The patient initiated chemotherapy in November 2012. He received 5 cycles of therapy, after which treatment with cisplatin had to be discontinued due to the reported deterioration of hearing. Once stable disease had been confirmed by CT, decision on continuation of treatment with pemetrexed was taken together with the patient. So far (June 2016), the patient has been on pemetrexed as monotherapy, achieving partial remission (PR), as defined by the RECIST criteria, as his best response to date (43 months of treatment). No significant adverse events have been reported.

DISCUSSION

Pleural mesothelioma is a rare disease with poor prognosis (1 case per 100 diagnoses of primary lung cancer) [4]. Establishment of the diagnosis is often a long and painstaking process. The histopathological diagnosis is made on the basis of thoracoscopy or open pleural biopsy, but with the use of traditional stains the microscopic picture is usually ambiguous, and immunohistochemistry assessment appears to be essential. It is also necessary to determine the histological type of the neoplasm, as it impacts the patient's prognosis. Pleural mesothelioma

has several histological types, including the epithelial, biphasic (mixed), sarcomatoid and desmoplastic ones. The disease is usually locally advanced, with rarely reported distant metastases. Unfavourable prognostic factors include old age, male gender, poor performance status, loss of body mass, the sarcomatoid histological subtype as well as elevated levels of white blood cells, platelets, and lactate dehydrogenase [4]. Radical treatment involves extrapleural pneumonectomy with the removal of half of the diaphragm and pericardium, followed by reconstructive surgery (mediastinoscopy should be performed at an earlier stage to determine the N2 involvement). Radical procedures also include simple and extensive pleurectomy, but they both carry a risk of non-radical resection [5]. Palliative surgical treatment consists in pleurectomy and palliative decortication as well as talc pleurodesis. Radiotherapy is symptomatic and used as part of palliative management. If surgical treatment is not an option, palliative chemotherapy is the treatment of choice. Pleural mesothelioma has a relatively low chemosensitivity, with cisplatin, antimetabolites (pemetrexed, ralitrexed and gemcitabine) and doxorubicin manifesting anticancer activity. It has been demonstrated that two-drug regimens are superior over monotherapy [6, 7]. Objective response is achieved in 14–40% of patients, with median overall survival (OS) amounting to 6–12 months. Patients qualified for chemotherapy should have a good performance status, without a significant loss of body mass. The epithelial histological subtype is the one that is considered favourable in terms of prognosis. Since 2003, standard first-line chemotherapy has been combined treatment with pemetrexed and cisplatin, with improved objective response rate (ORR – 40% vs. 16%), time to progression (TTP – 5.7 vs. 3.9 months), median overall survival (mOS – 12.1 vs. 9.3 months) and quality of life (QL) as compared to monotherapy with cisplatin [8]. Later studies indicated a similar efficacy of the two-drug regimen involving carboplatin and pemetrexed [9, 10].

In 2016, results of the MAPS phase III clinical trial were published in "The Lancet", demonstrating that adding bevacizumab, an antiangiogenic drug, to the PMT + DDP chemotherapeutic regimen as first-line treatment significantly prolongs overall survival as compared to the chemotherapy alone (mOS – 18.8 vs. 16.1 months) [11].

Sooner or later, however, all patients progress, be it during the first-line treatment or afterwards. There is no standard management in case of disease progression, following the first-line palliative chemotherapy in pleural mesothelioma. No adequately designed randomized clinical trial has yet been published that would prove the superiority of a cytostatic drug over placebo or BSC in patients with disease progression after the administration of the PMT + DDP regimen as first-line treatment. Only patients who have not received PMT at an earlier stage may be started on pemetrexed as second-line treatment according to a prospective randomized phase III trial of 2008, which demonstrated improvement of TTP and ORR as compared to best supportive care (BSC), with no impact on the overall survival, though. The lack of improvement in terms of OS might have stemmed from the fact that many patients from the BSC arm received PMT later into the treatment [12]. The above mentioned study, however, cannot be applied in contemporary clinical practice, as most probably every patient with advanced pleural mesothelioma receives PMT as first-line treatment as long as there are no contraindications to such management.

In patients who have received DDP + PMT as first-line treatment, accomplishing TTP of over 12 months, retreatment with PMT-based chemotherapy may be considered, if the patient in question has no contraindications to chemotherapy as such [13]. Vinorelbine and gemcitabine have been proven as active in the treatment of pleural mesothelioma, which is why the American NCCN (National Comprehensive Cancer Network) guidelines recommend the use of those drugs as second-line palliative chemotherapy [14]. A prospective one-arm study involving the use of once-weekly vinorelbine dosed at 30 mg/m^2 (6 weeks), demonstrated a 16% ORR and mOS of 9.6 months [15]. Another retrospective study, published in 2014, and dedicated to vinorelbine in the treatment of recurrent pleural mesothelioma (n = 59), demonstrated a 16% ORR, and mOS of around 6 months [16]. On the other hand, a retrospective analysis of 56 patients treated with vinorelbine, gemcitabine or a combination of the two, reported a 2% ORR and mOS of 5 months [17].

Attempts are being made at treating pleural mesothelioma with the use of antiangiogenic drugs, non-specific immunotherapy, and antibodies combined with cytostatics. Studies are currently under way [18–21]. Results of the phase III clinical trial involving an anti-CTLA-4 drug, tremelimumab, were presented at the last congress of ASCO (American Society of Clinical Oncology). The drug was administered to patients suffering from pleural mesothelioma (95% of the subjects) as second or third-line treatment in comparison to placebo. That large multi-centre study involved 571 patients, and failed to demonstrate a significant difference in terms of OS between the two study arms (mOS – 7.7 vs. 7.3). There is no data available on PFS and ORR yet (secondary endpoints) [22].

To sum up, the available second-line therapeutic options in patients with pleural mesothelioma are rather controversial. It appears reasonable that the patients be offered a chance to participate in clinical trials, whenever possible.

Due to the unsatisfactory treatment results in patients after progression of pleural mesothelioma, and based on their own observations, investigators from several centres have brought up the issue of maintenance therapy in patients who have not progressed during the first-line palliative treatment involving PMT + DDP. Such management is supposed to be aimed at maintaining the good response to treatment by continuing the administration of one of the drugs previously used as part of primary treatment (continuation maintenance) or by administering a new drug of proven efficacy (switch maintenance). However, it is believed that maintenance therapy prolongs chemotherapy, potentially increasing its toxicity, which is why the cytostatics used should have an acceptable toxicity profile, and should be well-tolerated with long-term use.

The concept of maintenance therapy is not a new one in pleural mesothelioma. As early as in the 90s, 2 small studies were published, involving the use of interferon α-2a or etoposide as maintenance therapy following the primary treatment with cisplatin [23, 24].

Cases of patients are described in the literature, in whom following induction chemotherapy, PMT was initiated as maintenance therapy, bringing about clinical benefits [25].

In 2006, a study was published, involving 27 patients who received maintenance PMT (13) or were only observed (14) after induction chemotherapy with DDP + PMT. Improvement was reported in terms of TTP (6 months vs. 3.4 months) and OS (17.9 vs. 8.5 months). The median number of PMT cycles was 4 (ranging from 2 to 14). In most cases, the reason behind the discontinuation of treatment was disease progression (70%) [26]. Since 2010, a randomized phase III trial has been under way, aimed at the assessment of PFS, OS, ORR, and treatment toxicity in patients receiving PMT as maintenance therapy (following primary induction chemotherapy with DDP + PMT, without disease progression) as compared to observation only. The study design provides for including over 130 patients in the trial, with preliminary data analysis scheduled for 2020 [27].

In 2013, "Lancet Oncology" published the results of the NVALT 5 randomized phase III trial, in which patients following induction chemotherapy with PMT (or with cisplatin or carboplatin), with no disease progression, were offered maintenance therapy involving a combination of thalidomide and BSC or BSC alone. Over 200 patients were qualified for the trial. TTP was the primary endpoint of the study. The study turned out to be negative (TTP 3.5 vs. 3.6 months) [28].

The present article discusses cases of patients in whom long-term survival has been accomplished thanks to the use of maintenance therapy with pemetrexed. Maintenance PMT was offered to the patients on account of the poor prognosis in pleural mesothelioma, lack of second-line treatment of proven efficacy, and the available results of the van den Bogaert study of 2006. All patients were in a good clinical condition throughout the therapy, despite the need for additional treatment of adverse events (diabetes) or delays in the consecutive chemotherapy cycles (renal insufficiency). Continuation of treatment was discussed with the patients at its every stage, with informed consent given at all times.

Pemetrexed maintenance therapy, with no disease progression after the administration of a standard two-drug regimen, is still an experimental treatment. There is evidence for the efficacy of such management in some selected patients only. It appears that in light of the lack of other second-line therapeutic options in case of disease progression, maintenance therapy may be considered in patients whose general condition is good, who do not suffer from the histologically unfavourable cancer type, and who benefitted from the two-drug palliative chemotherapy, and tolerated it well enough. However, the use of maintenance therapy, even when well-tolerated, always gives rise to a question of whether it would not be better to observe the patients involved, and administer appropriate therapy only at the time of disease progression. That question remains unanswered as of today. To the best of our knowledge, decision on maintenance therapy should be individualized and thoroughly discussed with the patient. There is a need for further prospective randomized studies, but the rarity of pleural mesothelioma remains a limiting factor.

CONCLUSIONS

The use of maintenance therapy with pemetrexed in the above described cases allowed us to achieve long-term survival in an advanced disease with poor prognosis. It should be emphasized, though, that the management discussed is an experimental treatment that requires further prospective randomized trials. Doctors and patients are now hopeful of the results of studies on new molecules (phase I trials) [18, 21]. Due to the low incidence of pleural mesothelioma, it is difficult to carry out studies with randomization, and a lot of information on the diagnosis and treatment of the neoplasm comes from prospective studies without randomization.

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Joanna Kardas: 80%
Agnieszka Buraczewska: 20%.