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Case report

Impressive remission in a patient with locally advanced malignant pleural mesothelioma treated with gemcitabine

M Weinmann, A Brandes, J Claßen, U Schott[1] and M Bamberg
Departments of Radiation Oncology and [1]Radiology, University of Tübingen, 72076 Tübingen, Germany.

The results of treatment of malignant pleural mesothelioma are quite unsatisfactory regardless of the substance or schedule employed. Although some activity is proved for anthracyclines, platinum compounds and alyklating substances, no chemotherapeutic regimen has emerged as a standard of care. Response rates documented in literature are between 10 and 20% for all these regimens. We report about a patient with locally advanced, unresectable pleural mesothelioma treated with the nucleoside analog gemcitabine (2,2-difluorodeoxycytidine). A 54-year-old male patient with unresectable pleural mesothelioma confirmed by thoracoscopic biopsy was treated with seven cycles of gemcitabine (1000 mg/m^2 on day 1, 8 and 15) over a period of 36 weeks. Restaging by thoracic computed tomography (CT) scan was performed after 8, 20 and 36 weeks. At week 36 after beginning of treatment, the CT scan exhibited a substantial partial remission with a reduction of tumor volume of over 50%. The adverse effects of the therapy were very moderate with a hematotoxicity not exceeding WHO grade I and a mild 'flu-like syndrome' during the first three cycles which responded quite well to steroids. The compliance of the patient was excellent and his general condition improved significantly under therapy. Gemcitabine seems to be an active drug for the treatment of pleural mesothelioma. Compared to other active regimens it is normally very well tolerated by the patients. Because of these characteristics gemcitabine seems a suitable antineoplastic substance, especially in palliative settings. It would be worthwhile to test its activity in pleural mesotheliomas in controlled trials.

Key words: Antineoplastic therapy, gemcitabine (2,2-difluorodeoxycytidine), malignant pleural mesothelioma.

Correspondence to M Weinmann, Department of Radiation Oncology, University of Tübingen, Hoppe-Seylerstrasse 3, 72076 Tübingen, Germany.
Tel: (+49) 7071 2982169; Fax: (+49) 7071 295609;
E-mail: martin.weinmann@uni.tuebingen.de

Introduction

Malignant mesothelioma is an aggressive malignancy with very poor prognosis regardless of the treatment modality employed. Median patient age at diagnosis is 60 years, and median survival after diagnosis ranges between 4 and 18 months in various series. Good prognostic factors are epithelial histology, good performance status and younger age, but even among this subgroup few if any patients can be cured.

Most of the reported cases are associated with asbestos exposure, but in between 30 and 50% of all cases patients have no history of asbestos exposure.[1] The latency period between exposure and diagnosis is between 30 and 35 years.

Surgery, radiotherapy, chemotherapy and combined approaches as well as best support care alone have been used for treatment.[2]

Surgical management can be performed with curative or palliative intention. Very few patients in early stages and a good condition are suitable for curative surgical therapeutic strategies like extrapleural pneumectomy, and up to 80% of the patients undergoing pleurectomy have residual disease left behind after this procedure. So, despite this agressive therapeutic approach including a high perioperative mortality between 5 and 20%, less than 20% of these patients remain free of disease after 3 years and the 5 year overall survival is almost zero. Even in this selected subgroup of patients eligible for extrapleural pneumectomy the median survival in various studies ranges between 9 and 19 months after the procedure.[2] Pleural decortication as a palliative modality alone is performed to control or prevent pleural effusion and exhibits similar survival rates.

Similar to the surgical approaches, the efficiency of radiotherapy in terms of improved survival remains uncertain in the treatment of malignant mesothelioma.

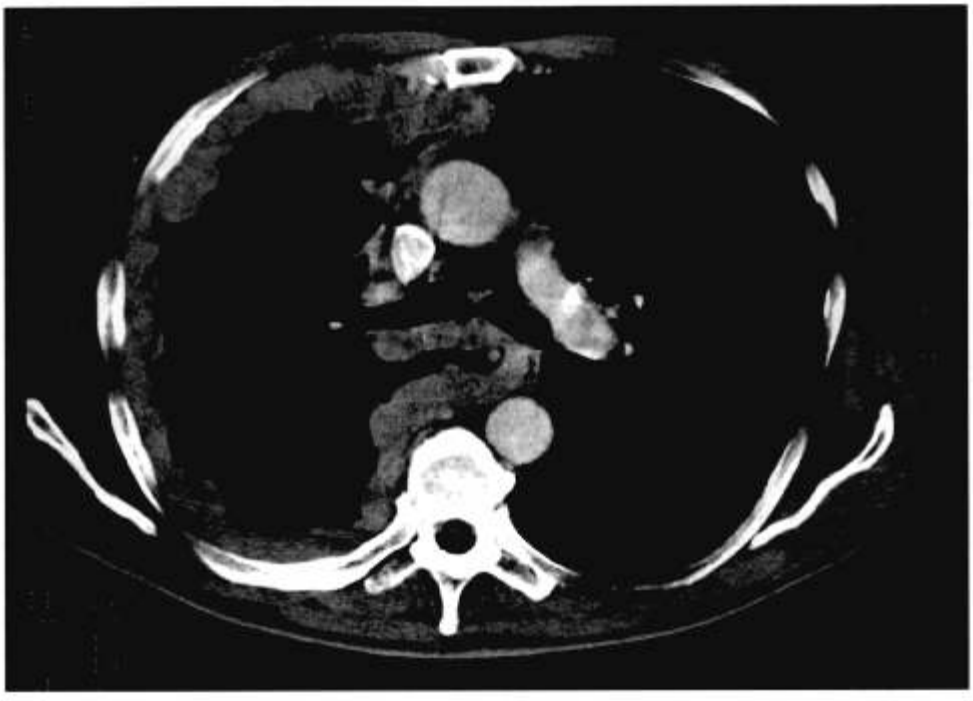

Figure 1. Contrast-enhanced chest CT prior to initiation of systhemic treatment. The entire inner wall of the right thorax is covered by an irregulary shaped tumor with only moderate contrast enhancement corresponding to the histologically proven malignant mesothelioma.

Doses between 40 and 55 Gy to the entire pleura with local enhancement of radiation dose on bulky regions are mandatory for local tumor control. If radiotherapy is used as a definite treatment, the target volume would encompass the entire ipsilateral pleura, the diaphragma and parts of the mediastinum. No survival benefit has been proved even for such agressive radiotherapeutic strategies. So the use of radiotherapy is merely palliative, because it is often impossible to deliver curative doses to the pleura without deleterious damage to the lung. Relief of pain and dyspnoe is described in a substantial portion of patients when a dose of at least 40 Gy has been applied.[3] Especially in the case of bulky tumors, some studies document a significant release of symptoms but no impact on the survival rate.[4]

The current lack of curative approaches underlines the importance of active antineoplastic substances for an efficient palliative chemotherapy. Although numerous agents, such as anthracycline derivates, alkylating agents, plant alkaloids and related compounds, antimetabolites, and biological response modifiers, have been tested in pleural mesothelioma, no chemotherapeutic regimen has emerged as a standard of care up to now.[3,5-7]

No data have been published yet concerning the activity of gemcitabine (2,2-difluorodeoxycytidine) in malignant pleural mesothelioma. Gemcitabine is a fluorine-substituted cytarabine analog with activity against a wide range of solid tumors. In animal models gemcitabine has shown activity against colon, head and neck, breast, lung, pancreatic, ovarian, gastric, and liver carcinomas.[8,9] Also, a variety of phase I and phase II trials have been published in patients with breast cancer, non-small cell lung cancer, small cell lung cancer, pancreatic cancer, epithelial ovarian cancer and bladder cancer.[10]

The promising results of gemcitabine in a wide variety of solid tumors, and its acceptable and moderate toxicity profile, was the rationale to test its activity in a patient with local advanced malignant mesothelioma.

Patient and methods

This is a case report about a patient with malignant pleural mesthelioma treated with gemcitabine at the Department of Radiation Oncology, University of Tübingen between June 1997 and February 1998. In June 1997 a 54-year-old male patient with advanced pleural mesothelioma was admitted to our hospital. He

had a history of recurrent pleuritis and pleural effusions since 1985. Thoracoscopic biopsy in 1990 exhibited no malignancy.

After ongoing complaints a thoracoscopy was performed in September 1996 and multiple biopsy specimens were taken, which confirmed the diagnosis of a malignant pleural mesothelioma of the epithelial subtype. A prior exposure to asbestos could not be demonstrated. The patient had no other severe medical disorders in his history. At the time of diagnosis the tumor already involved main parts of the right visceral and parietal pleura, and invaded the diaphragma and the mediastinum. So even with a radical surgical approach involving extrapleural pneumectomy, and resection of pericard and diaphragma no complete resection would have been achieved. The tumor was neither considered as resectable nor as appropriate for definitive radiotherapy. At the time of diagnosis the patient had only mild symptoms, such as moderate weight loss, sleep disorders, a mild dyspnoe during activity, but no thoracic pain, so he received no specific treatment at that time.

Six months prior to admission to our hospital his general condition deteriorated with increasing dyspnoe, fatigue and a weight loss of 8 kg within 6 months.

Thoracic computed tomography (CT) in March 97 showed a significant progress of the tumor with increasing pleural and mediastinal masses, and extension to the liver and the mediastinum with compression of the oesophagus (Figure 1). According to the TNM staging system he presented with stage T4 N1 M0 or stage IV according to the staging system of the International Mesothelioma Interest Group (IMIG).[11] The Karnofsky index was about 70 according to the Karnofsky performance scale.

So on 18 June we started palliative chemotherapy with a 30 min i.v. infusion of 1000 mg/m^2 gemcitabine on day 1, 8, and 15. Each cycle was repeated after 4 weeks.

Antiemetic prophylaxis was performed with 5 mg of tropisetrone as a short i.v. infusion 20 min prior to chemotherapy and in cycle 4–6 4 mg of dexametasone i.v. on day 1 and orally on the following 2 or 3 days was added.

At baseline we performed standard laboratory testing, ECG and a chest X-ray. Staging was completed with abdominal ultrasound, abdominal CT scan and a ^{m99}Tc-bone scan. There was no clinical or radiographic evidence for metastatic lesions. Baseline laboratory values were normal except for an elevation of C-reactive protein up to 40 mg/l and a hemoglobin value of 11.6 g/100 ml. Hematologic adverse effects were monitored by weekly blood counts and prior to each application of gemcitabine liver enzymes, and retention values were evaluated.

Between June 1997 and February 1998 the patient received seven cycles of gemcitabine.

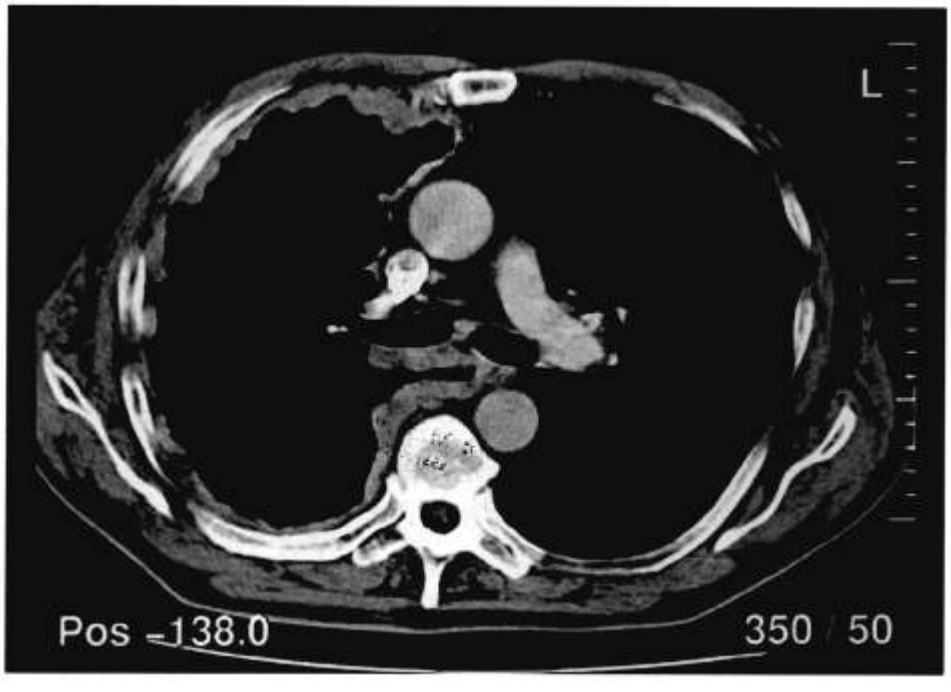

Figure 2. Contrast-enhanced chest CT in the corresponding slice position to Figure 1. After application of seven cycles of chemotherapy with gemcitabine the tumor had shrunk to approximately 50% of the initial volume.

Results

Under the first two cycles of gemcitabine his general condition stabilized and no further weight loss occurred. This clinical impression was confirmed by a thoracic CT scan for re-staging 8 weeks after the beginning of the treatment. The CT scans showed a stable disease with no further tumor progression. The antineoplastic treatment was continued for another two cycles. In week 20 after the beginning of the treatment, thoracic CT scans exhibited a regression of the nodular tumor masses on the right pleura. We applied another three cycles of gemcitabine and re-evaluated this treatment in February 1998 in week 36. These scans confirmed a partial remission with over 50% reduction of tumor volume (Figure 2). Altogether seven cyles of gemcitabine have been applied from June 1997 to February 1998. During the first three cycles the general condition of the patient stabilized and he improved significantly during the subsequent four cycles until February 1998. The body weight increased from 78 kg in June 1997 to 86 kg in February 1998 and also his dyspnoe improved significantly. Between February and June 1998 his general condition was stable and thoracic CT performed in May 1998 exhibited no change compared to February.

The compliance of the patient was excellent and the adverse effects of the treatment were very moderate. No dose reduction or delay of the schedule was necessary. During the first three cycles the patient developed a flu-like syndrome with temperatures up to 39.1°C, chills and myalgia. These symptoms improved after adding 4 mg dexametasone per day on day 1-3 after treatment and during cycle 4-7 only subfebrile temperature occured occasionally 3-4 days after chemotherapy. He developed nausea but no vomiting during these first three cycles, but these symptoms improved after adding dexametasone.

We observed no relevant myelosuppression under therapy and all blood counts were normal during the whole treatment. There was no evidence of any cutaneous, pulmonary, neurological, cardial or renal adverse effects nor significant alopecia. ECG was unchanged compared to the baseline examination.

Discussion

Reported median survival times for patients of unresectable mesotheliomas are in the 6-12 months range with supportive care alone, but most of the phase II chemotherapeutic regimen have shown no or only little benefit over supportive care alone in terms of median survival rate. The response rates are usually under 20%. Older data from the 'pre-CT era' are difficult to interpret, because the extent of the tumor is difficult to measure by conventional X-rays and so response rates evaluated by chest X-rays are uncertain.[4]

Single-agent studies have been performed with anthracycline derivates (doxorubicin, THP-doxorubicin, pirarubicin, epirubicin, detorubicin, actinomycin D, menogaril, mitoxantrone, diaziquone), with alkylating agents (cyclophophamide, ifosphamide, mechlorethamine, thiotepa, melphalan, procarbazine, mitomycin C, cisplatin, carboplatin, iproplatin), with plant alkaloids and related compounds (paclitaxel, vincristine, vindesine, etoposide), with antimetabolites (5-fluoruracil, high-dose methotrexate, dideazafolic acid, 5-azacytidine, acivicin, bleomycin, trimetrexate) and some other substances like biological response modifiers [Bacille Calmette-Guerin, p30 protein, interferon (INF)-α, INF-β, INF-γ, interleukin-2], or miscellaneous antineoplastic substances like amsacrine or cyclolencine.[2,5-7]

Few of these agents have shown a clear benefit regarding quality of life or median survival rates and the response rates are fairly low. In the past, many small studies have reported encouraging data, but such favorable outcomes have usually not been confirmed by larger series. Due to the infrequency of the disease most of these studies were on a small number of patients.

Antracyclines and especially doxorubicin have been considered as active substances, although reponse rate is low and varies between 0 and 26%.[5,12] Other DNA intercalating agents including mitoxantrone, amsacrine or actinomycin D showed no significant activity *in vivo*.[3,6,7] Cisplatin and carboplatin have been tested in five large trials. Doses between 100 and 120 mg/m^2 cisplatin every 4-6 weeks produced response rates of 13 or 14%.[13] Higher response rates of 36% have been reported in a small trial of 14 patients using dose-intensified platinum (80 mg/m^2 weekly) for 6 weeks.[14] Plant alkaloids like the vinca alkaloid vincristine or vindesine or members of the taxane group had no significant activity.

Alkylating agents like cyclophosphamide or ifosfamide have shown minor activity in clinical trials. Four larger trials using single-agent ifosfamide reported response rate between 3 and 24%. These differences might derive from a dose-reponse effect with a 2.5-fold increased response rate in the higher dose group, but at the cost of significant myelotoxicity.[5] Cyclophosphamide produced no response in a trial with 16 patients.[15]

Combination chemotherapy regimens have been also tested in mesothelioma but showed no clear

advantage, usually being asscociated with higher toxicity. Most of these regimens are either based on doxorubicin or platinum. The results of these studies indicate that combination chemotherapy cannot be recommended over the use of single-substance chemotherapy except under study conditions. At the moment anthracycline derivates, ifosfamide or platinum compounds are considered as first-line drugs.[6,13]

Against the background of the current unsatisfactory therapeutic situation in advanced malignant mesothelioma, gemcitabine seems to us promising for two reasons. First, it has been tested against a wide variety of different solid tumors, and its cytotoxic activity has been proven *in vitro* and *in vivo*. Secondly, its toxicity profile derived from a lot of phase I and II studies is moderate compared to other drugs. It seems especially suitable in palliative settings, primarly aimed at improving the quality of life.

A weekly schedule for 3 weeks with single doses between 750 and 1200 mg/m^2 administered as a 30 min infusion followed by 1 week of rest has been established as a standard scheme. Myelosuppression, especially thrombocytopenia, is normally the dose-limiting toxicity.

With this schedule the drug is well tolerated with major toxicity being moderate and short-lived myelosuppresssion, fatigue and in up to 20% of all cases a mild flu-like syndrome. Mucositis and alopecia is rare and nausea and vomiting mild. Other less common toxicities are somnolence, diarrhea, constipation and transient dyspnoe. In about 20% of all patients peripheral edema without any signs of cardiac hepatic or renal failure occurs. Transient rises in liver enzymes, mild proteinuria and hematuria are common, but rarely of clinical significance. Only in a few cases has renal failure of uncertain etiology been reported. Of nearly 11 000 protocol-defined injections, 94% could be administered and only 15.4% dose reductions have been necessary. To conclude, gemcitabine is well tolerated compared to other substances.[16]

References

1. McDonald AD, McDonald JC. Epidemiology of malignant mesothelioma. In: Antman K, Aisner J, eds. *Asbestos related malignancy*. Orlando: Grune & Stratton 1987: 31-50.
2. Antman KH, Schiff PB, Pass HI. Benign and malign mesothelioma. In DeVita V, Hellman S, Rosenberg SA, eds. *Cancer—principles and practice of onology*, 5th edn. Philadelphia: Lippincott-Raven 1997: 1853-78.
3. Gordon W, Antman KH, Breeberger J, Weichselbaum R, Chaffey J. Radiation therapy in the management of patients with mesothelioma. *Int J Radiat Ther Biol Phys* 1982; **8**: 19-26.
4. Schiebe M, Hoffmann W, Kortmann RD, Bamberg M. The clinical picture and therapy of malignant pleural mesothelioma. *Strahlenther Onkol* 1994; **170**: 628-35.
5. Ryan CW, Herndon J, Vogelzang NJ. A review of chemotherapy trials for malignant mesothelioma. *Chest* 1998; **113** (suppl): 66-73.
6. Taub RN, Antman KH, Chemotherapy for malignant mesothelioma. *Semin Thorac Card Surg* 1997; **9**: 361-6.
7. Tiong Ong S, Vogelzang NJ. Chemotherapy in malignant pleural mesothelioma: a review. *J Clin Oncol* 1996; **14**: 1007-17.
8. Braakhuis BJM, Van Dongen JB, Vermorken JB. Preclinical *in vivo* activity of 2,2-difluorodeoxycytidine (gemcitabine) against human head and neck cancer. *Cancer Res* 1991; **521**: 211-4.
9. Hertel LW, Boder GB, Kroin JS. Evaluation of the antitumor activity of gemcitabine (difluoro-2-deoxycytidine). *Cancer Res* 1990; **50**: 4417-22.
10. Kaye SB. Gemicitabine: Current status of phase I and II trials (editorial). *J Clin Oncol* 1994; **12**: 1527-8.
11. Rusch VW and the International Mesothelioma Interest Group. A proposed new international TNM staging system for malignant pleural mesothelioma. *Chest* 1995; **108**: 1122-8.
12. Krarup Hansen A, Hansen HH. Chemotherapy in malignant mesothelioma. *Cancer Chemother Pharmacol* 1991; **28**: 319-30.
13. Mintzer DM, Kelsen D, Frimmer D, *et al.* Phase II trial of high dose cisplatin in patients with malignant mesothelioma. *Cancer Treat Rep* 1985; **69**: 711-2.
14. Planting A, Goey H, Verweij J. A phase II study of six weekly courses of high dose cisplatin in mesothelioma. *Proc Am Ass Cancer Res* 1991; **32**: 194 (abstr).
15. Sorensen PG, Bach F, Bork E, *et al.* Randomized trial of doxorubicin versus cycolphosphamide in diffuse malignant pleural mesothelioma. *Cancer Treat Rep* 1985; **69**: 1431-2.
16. Aapro MS, Martin C, Hatty S. Gemcitabine—a safety review. *Anti-Cancer Drugs* 1998; **9**: 191-201.

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