Cancer Chemother Pharmacol (2000) 45: 177–181

CLINICAL TRIAL REPORT

Ofer Merimsky · Isaac Meller · Gidon Flusser
Yehuda Kollender · Josephine Issakov
Miriam Weil-Ben-Arush · Eyal Fenig
Gad Neuman · Dov Sapir · Shmuel Ariad
Moshe Inbar for the Israeli
Soft Tissue and Bone Sarcoma Treatment Groups

Gemcitabine in soft tissue or bone sarcoma resistant to standard chemotherapy: a phase II study

Received: 10 June 1999 / Accepted: 7 September 1999

Abstract *Purpose*: To assess the efficacy of gemcitabine in patients with a variety of sarcomas that have failed to respond or escaped Adriamycin- and ifosfamide-based chemotherapy. *Patients and methods*: A group of 18 symptomatic heavily pretreated patients with sarcomas of bone or soft tissue received one induction course of gemcitabine at a dose of 1000 mg/m^2 per week for 7 consecutive weeks, followed by 1 week rest. Response to the induction course was assessed by interview and by repeated ancillary tests. If no progression was observed, maintenance by gemcitabine 1000 mg/m^2 per week for 3 weeks every 28 days was given until failure was clinically or radiologically evident. *Results*: A total of 51 cycles of gemcitabine were given including 18 cycles of induction. A mean of 3.6 postinduction cycles were given to nine patients. The treatment was well tolerated by the patients. One partial response (leiomyosarcoma) and one minimal response (angiosarcoma) were observed, yielding a true objective response rate of 5.5%. An additional six patients achieved stabilization of disease (chondrosarcoma and osteosarcoma), yielding an overall progression-free rate of 44%. The median time to progression was more than 27 weeks. Clinical benefit response was observed only in those who also achieved a progression-free state. *Conclusion*: Gemcitabine was found to be effective in achieving stabilization and even a minimal response of soft tissue or bone sarcoma refractory to standard chemotherapy.

Key words Gemcitabine · Soft tissue sarcoma · Bone sarcoma · Angiosarcoma · Leiomyosarcoma

O. Merimsky (✉) · M. Inbar
Department of Oncology, The Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv 64239, Israel
e-mail: merimsky@internet-zahav.net
Fax: +972-3-6974828

I. Meller · Y. Kollender
National Unit of Orthopedic Oncology, The Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

G. Flusser
Department of Radiology, The Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

J. Issakov
Department of Pathology, The Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

M. Weil-Ben-Arush
Department of Pediatric Oncology, Rambam Medical Center, Haifa, Israel

E. Fenig
Department of Oncology, Rabin Medical Center, Petach-Tiqua, Israel

G. Neuman
Department Pediatric Oncology, Sheba Medical Center, Tel-Hashomer, Israel

D. Sapir
Department Oncology, Haemek Medical Center, Afula, Israel

S. Ariad
Department of Oncology, Soroka Medical Center, Beer-Sheva, Israel

Introduction

Gemcitabine hydrochloride (2′,2′-difluorodeoxycytidine hydrochloride, Gemzar; Eli Lilly, Indianapolis, Ind.) is a pyrimidine nucleoside analog used as a chemotherapeutic antimetabolite. Although gemcitabine is similar in structure to cytosine arabinoside, it exhibits different characteristics and pharmacology which enhance its usefulness in the treatment of patients with solid tumors. Gemcitabine inhibits DNA replication by inhibiting DNA synthesis and by blocking repair mechanisms through masked chain termination. Additionally, gemcitabine exerts several other actions that self-potentiate its cytotoxic activity. Gemcitabine is usually well tolerated by the patients and its common associated side effects are not severe, and include low-grade myelotoxicity, 'flu-like syndrome, fever, rash, swelling of the legs,

and nausea and vomiting. Gemcitabine has demonstrated significant clinical activity and clinical benefit response in a variety of tumors including pancreatic, ovarian, breast, bladder, non-small cell lung (NSCLC), and small-cell lung cancer [1–4].

Very scarce data are available on the use of gemcitabine in soft tissue sarcomas (STS) or bone sarcomas. Gemcitabine has been found to be active against xenografts of STS growing in nude mice [5, 6]. Palliative effects of gemcitabine in a patient with osteosarcoma resistant to standard chemotherapy [7] have recently been reported by our team. We report our experience with gemcitabine in patients with a variety of sarcomas that had failed to respond to chemotherapy based on doxorubicin (Adriamycin, ADR) and ifosfamide (IFX).

Patients and methods

Eligibility

Eligibility criteria were recurrent or metastatic osteosarcoma, chondrosarcoma or STS, that had either failed to respond to standard chemotherapy for metastatic or recurrent disease and progressed while on chemotherapy, or relapsed after having been treated with preoperative or adjuvant chemotherapy and had demonstrated progressive disease over a period of 4–8 months. Standard chemotherapy for STS must have included ADR and IFX. Standard chemotherapy for bone sarcoma had to have included methotrexate (MTX), cisplatin (CDDP), ADR and IFX. Patients with chondrosarcoma could be chemo-naive, but had to have disease progression and aggravation of symptoms. All the patients had to be 15 years of age or older, with a Karnofsky's performance status (KPS) of at least 40%, and life expectancy of at least 3 months. Any sarcoma type was permitted provided that there was measurable disease, and there was no central nervous system or spinal cord involvement. Signed informed consent was mandatory (in the case of patients younger than 18 years, parents also signed).

Treatment protocol

Baseline evaluation included interview and assessment of symptom severity and quality of life, measurement and documentation of marker lesions by CT scan, ultrasound or plain X-rays, and complete blood count and biochemical serum analysis.

Treatment consisted of induction by gemcitabine 1000 mg/m^2 per week for 7 consecutive weeks, followed by 1 week rest. Response to the induction course was assessed by interview (for clinical benefit response and quality of life) and by repeated ancillary tests. If no progression was observed, maintenance by gemcitabine 1000 mg/m^2 per week for 3 weeks every 28 days was given until failure was clinically or radiologically evident. Evaluation of response, toxicity and quality of life was performed every 3 months by interview, physical examination, and ancillary tests, according to the WHO criteria. Progression was determined as deterioration in clinical symptoms, appearance of new lesions or enlargement of a lesion by at least 25% of its pretreatment size. Treatment was to be stopped in case of life-threatening toxicity, progression of the disease, or on patient's refusal to continue.

Patients

A total of 18 patients (7 females, 11 males; age range 15 to 62 years, median 40 years) were enrolled from December 1996 through August 1998. Ten patients had primary extremity sarcoma, and eight had primary tumors arising elsewhere in the body (trunk, head and neck region, or unknown primary site). There were six patients with osteosarcoma, one with Ewing's sarcoma, three with chondrosarcoma and eight with STS, of whom two had leiomyosarcoma, two had liposarcoma, two had malignant fibrous histiocytoma, one had angiosarcoma and one had alveolar soft part sarcoma (ASPS). Only one patient with chondrosarcoma was chemo-naive, the remaining 17 having been heavily pretreated by various agents according to their disease, such as ADR, IFX, high-dose IFX, MTX, and etoposide. The involved sites were mainly the local tumor bed and lung. The related symptoms were pain in 17 patients, and respiratory problems, mainly cough and dyspnea, in 5. Patient characteristics are detailed in Table 1.

Results

A total of 51 cycles of gemcitabine were given including 18 cycles of induction. Three patients received only a partial induction cycle due to unexpected disease progression and drop in the KPS to below 40%. Six patients received only induction cycles and were excluded due to lack of objective response and clinical benefit response. A mean of 3.6 postinduction cycles were given to nine patients. In one of the nine, three postinduction courses were needed in order to determine lack of clinical benefit response, although it was clear that there was no objective change in the disease pattern (Table 1).

One partial response (leiomyosarcoma of the uterus) and one minimal response (angiosarcoma of the scalp) were observed, yielding an objective response rate of 1/18 (5.5%). If minimal response is also considered as true response, the rate was 11%. An additional six patients achieved stabilization of disease which was rapidly progressing prior to gemcitabine administration (chondrosarcoma and osteosarcoma), yielding an overall disease-control rate of 8/18 (44%). Time to progression ranged from 8 to 86 weeks. The median time to progression was more than 27 weeks. Clinical benefit response (improvement of performance status, alleviation of respiratory symptoms, alleviation of pain and reduction in narcotic consumption) was observed only in those who also achieved a progression-free state.

None of the patients who failed to respond to gemcitabine had any clinical benefit response. The treatment was well tolerated by the patients. Hematological toxicity was the main concern in this group of patients, of whom the vast majority were heavily pretreated (Table 2). Other toxic effects included weakness in nine patients, rash in one, ascites (no malignant cells in repeated taps) in one, limb edema (deep vein thrombosis was excluded by Doppler-ultrasound study) in one, and low-grade fever in two.

Discussion

STS and bone sarcomas carry a poor prognosis. Close to one-half of patients succumb to metastatic or locally advanced disease. Metastatic sarcoma is usually fatal

Table 1 Patients' data and results of treatment with gemcitabine (Histology: *ASPS* alveolar soft part sarcoma; *MFH* malignant fibrous histiocytoma. Previous treatments: *ADR* Adriamycin; *AI* Adriamycin 50 mg/m^2 on day 1 plus ifosfamide 5 g/m^2 given continuously over 48 h; *Bleo* bleomycin; *CIS* cisplatin; *CTX* cyclophosphamide; *HDIFX* high-dose ifosfamide (12 g/m^2 given continuously over 72 h); *ICE* ifosfamide, carboplatin, etoposide; *IFN* interferon; *IFX* ifosfamide; *IFX-Vp* ifosfamide, etoposide; *MAID* mesna, Adriamycin, ifosfamide, dacarbazine; *MID* MAID without Adriamycin (omitted due to drop in left ventricular ejection fraction); *MTX* methotrexate; *OP* surgery; *RT* radiation therapy; *TXTR* Taxotere; *VAC-VpI* vincristine, Adriamycin, cyclophosphamide alternating with etoposide and ifosfamide (protocol for Ewing's sarcoma); *Vp16* etoposide. Response: *CBR* clinical benefit response; *MR* minimal response; *PD* progressive disease; *PR* partial response; *SD* stable disease

Patient initials	Sex	Age (years)	Site of primary	Histology	Previous treatments	Involved sites	KPS (%)	Symptoms	No. of cycles given	Response to gemcitabine	Time to progression (weeks)
BM	M	54	Arm	MFH	MAID, MID, HDIFX	Lungs	70	Cough	1	PD, no CBR	0
MC	F	45	Gluteus	Liposarcoma	AI	Local recurrence	40	Pain	0, 14	PD, no CBR	0
AE	M	27	Pelvis	Ewing's sarcoma	VAC-VpI	Local, lungs	70	Pain	0, 3	PD, no CBR	0
OY	M	52	Sacrum	Chondrosarcoma	OP, RT, AI	Local, lungs	70	Pain	1	PD, no CBR	0
DD	M	36	Thigh	Round-cell liposarcoma	AI	Lungs	70	Pain	1	PD, no CBR	0
LI	M	45	Skin	Leiomyosarcoma	AI	Liver, skin, adrenal	60	Abdominal pain, weakness	0, 5	PD, no CBR	0
ZS	F	60	Scalp	MFH	OP, RT, AI	Face, scalp, orbit, skull	70	Pain, cosmetic deformity	1	PD, no CBR	0
HO	M	25	Femur	Osteosarcoma	CIS, ADR, MTX, HDIFX	Lung	70	Pain, cough	1	PD, no CBR	0
KA	M	24	Femur	Osteosarcoma	CIS, ADR, MTX, HDIFX	Local, lungs	40	Pain, dyspnea	1	PD, no CBR	0
AZ	F	24	Thigh	ASPS	AI	Lung, bone	50	Pain, dyspnea	4	PD, no CBR	0
SD	F	44	Thigh	Chondrosarcoma	OP	Thigh, pelvis	50	Pain	2	SD, less pain	8
SO	F	15	Femur	Osteosarcoma	CIS, ADR, MTX, HDIFX, IFX-Vp	Local	50	Pain	4	SD, less pain, KPS 80%	13
SE	M	60	Thigh	Chondrosarcoma	Hemipelvectomy, oral Vp16	Pelvis, retroperitoneum	40	Pain	3	SD, less pain	16
AY	M	18	Femur	Osteosarcoma	CIS, ADR, MTX, HDIFX, IFX-Vp, Bleo, CTX, OP	Lung, bone	70	Pain	4	SD, CBR, KPS 80%	16+
KY	M	62	Scalp	Angiosarcoma	OP, RT, IFX, ADR, IFN, TXTR	Face, scalp, orbits, lymph nodes	60	Pain, wounds, swelling of face	5	MR, CBR, KPS 70%	38+
ES	F	48	Uterus	Leiomyosarcoma	AI, ICE, OP	Lung, liver, thigh	70	Pain in the leg	6	PR (lung, liver, thigh), CBR	39+
GI	M	22	Femur	Osteosarcoma	OP, CIS, ADR, MTX, HDIFX	Lung	70	Cough, pain	8	SD, CBR, KPS 80%	42
VR	F	28	Pubis	Osteosarcoma	OP, CIS, ADR, MTX, HDIFX, Vp	Local	50	Pain	8	SD, CBR, KPS 70%	96

Table 2 Hematological toxicity related to treatment with gemcitabine (WHO scale)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hb	13	1	2	2	0
Neutrophils	12	0	3	3	0
Platelets	7	3	5	3	0

and treatment options are rather limited. Median survival from the time metastases are detected is relatively short, although 20–25% of patients with metastatic sarcoma are alive 2 years after diagnosis.

Patients with metastatic sarcoma often are asymptomatic at the time that a radiograph or CT reveals metastases, and may remain free of symptoms for long periods of time. Thus, alleviation of symptoms is not an immediate concern in many patients, although disease progression is eventually inevitable. The arsenal of chemotherapeutic drugs active against metastatic sarcoma is limited to ADR, IFX, etoposide, CDDP, MTX and dacarbazine (DTIC). The activity of commonly used chemotherapeutic agents in patients with STS is moderate, and the observed response rate is about 30%.

A variety of combination chemotherapy regimens have been studied in phase II trials. Most combinations include ADR and an alkylating agent. Overall, response rates are higher in these single-arm trials than in larger, randomized studies. The combination of ADR and DTIC (AD) yields 41% major responses. The CyVADIC regimen (cyclophosphamide, vincristine, ADR, DTIC) was widely accepted as the standard of care for over a decade. In trials of variations of this four-drug combination, responses have ranged from 38% to 71%, The MAID regimen (mesna, ADR, IFX, DTIC) consisting of the three antineoplastic agents with activity against STS, yielded an overall response of 47% in a large phase II trial [8]. After failing in MAID or CyVADIC combinations, there is eventually no more to offer the patients except for investigational drugs. The patients, especially the younger, may still have considerable life expectancy and good performance status, and are eager to be treated, but the caring oncologist may have nothing to propose. There is a need for active and minimally toxic agents that can be given as second-line treatment in patients with STS or bone sarcomas. This was the rationale to use gemcitabine in this hopeless population of patients with sarcoma.

The information given to patients before participation in such study, especially when no more standard therapy exists for young patients with a strong life will, should give "controlled hope" but without the illusion of cure. The patients were told that gemcitabine was purely experimental in sarcoma, that there was no literature on the topic, that the worldwide experience with the drug was achieved in other diseases, and that the expected toxicity was relatively mild.

Our results point to important efficacy and a possible role for salvage of gemcitabine treatment in heavily pretreated patients with progressive STS or bone sarcomas. Gemcitabine was found to be effective in achieving stabilization and even a minimal response of STS (uterine leiomyosarcoma and scalp angiosarcoma) or osteosarcoma refractory to standard chemotherapy consisting mainly of ADR, high-dose MTX, CDDP and IFX. Although disease stabilization is generally accepted as failure of chemotherapy, in this series of cases it should be regarded as success due to noteworthy disease control, clinical benefit response, and low toxicity profile, especially in view of failure of accepted drugs.

It is interesting to note that in a recent study reported by Patel et al. [9], patients with various types of STS were given gemcitabine in a schedule similar to that used in our trial. The best responses were observed, as in our study, in patients with angiosarcoma and leiomyosarcoma. The observations in these trials point to a possible role of gemcitabine in the treatment of angiosarcoma and leiomyosarcoma.

In our study and in the study by Patel et al., gemcitabine monotherapy was given in a schedule of 1 g/m^2 per week for 3 weeks every 28 days. A different schedule has been suggested by Spith-Schwalbe et al. [10]: 200 mg/m^2 given on days 1, 8, and 15 by 6-h continuous infusion every 28 days. In their study 11 heavily pretreated patients with STS were enrolled. The side effects were mainly hematological, and the response, i.e. two partial responses and three disease stabilizations, were all in pulmonary metastases. The optimal schedule for administration of gemcitabine in sarcomas is yet undetermined.

Gemcitabine affected, to various extents, the course of the disease in patients with several types of sarcoma. Three out of six treated osteosarcomas, two out of three treated chondrosarcomas, one out of two treated leiomyosarcomas and one angiosarcoma changed their progressive course into stabilization or regression. Postponing the inevitable death with a relatively nontoxic treatment is an important issue especially in young patients.

It is clear that no treatment recommendations can be made on the basis of such a small series. However, it may be justified and warranted to investigate the activity of gemcitabine in a larger group of patients with sarcomas, particularly in osteosarcoma and leiomyosarcoma, even as a first-line treatment for recurrent or metastatic disease. Such a trial is already ongoing.

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