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Activity of thalidomide in patients with platinum-refractory germ-cell tumours

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ABSTRACT

The aim of this study was assess the activity of thalidomide in patients with progressive relapsed or platinum-refractory germ-cell tumours (GCT). Between April 2002 and January 2003, 15 patients with inoperable progressive GCT were treated with escalated daily doses of 200–600 mg thalidomide. All patients had failed first-line and salvage chemotherapy with a median of 6 (range 4–12) cisplatin-based treatment cycles, 13/15 (87%) patients had received high-dose chemotherapy (HDCT) and 8/15 (53%) patients were considered platinum-refractory or absolute refractory; 8/15 (53%) patients had previously received other palliative chemotherapy regimens. No patient achieved a complete remission (CR) or partial remission (PR). However, 5/15 (33%) patients achieved serological PR and 1 additional patient had stable disease for 3 months. The median duration of remissions was 3 months (range 2–12 months) including 2 patients with a progression-free survival of 9 and 12 months. Responses occurred mainly in patients with a low tumour burden, slow disease progression and alpha-foetoprotein (AFP) elevations. Responses to thalidomide were independent from platinum-sensitivity. Toxicity was mild, with lethargy and constipation in the majority of patients. Skin rash grade II developed in 2 patients and peripheral neurotoxicity grade II/III developed in 4 patients. One responding patient died suddenly from an unknown cause. It is concluded that thalidomide shows single-agent activity in patients with heavily pretreated GCT, AFP elevations and slowly progressive disease.

1. Introduction

Patients with germ-cell tumours (GCT) who relapse or progress after adequate conventional-dose or high-dose salvage-chemotherapy have a poor prognosis. Some patients profit from aggressive surgical removal of chemotherapy-refractory tumours ('desperation surgery').[1] In inoperable patients further chemotherapy may be used for palliation. Oral etoposide, paclitaxel, gemcitabine and oxaliplatin, or combinations of these agents, have recently been investigated in phase I/II studies and have shown response rates of 15–20% in this patient population.[2–4] However, despite these treatments even responding patients eventually progress and die.

Thalidomide has shown activity in various tumours. It has anti-angiogenic properties, presumably due to inhibition of the vascular endothelial growth factor (VEGF) receptor, but also exhibits immunomodulatory and even direct cytotoxic effects.[5–7] Its exact mode of action, however, is not known.

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2. Patients and methods

2.1. Patients

From April 2002 through January 2003, a total of 15 patients with GCT were enrolled. All patients signed written informed consent forms prior to participation in the trial. The study was approved by the ethics committee of the Humboldt-University, Charité Campus Mitte, Berlin, Germany.

Eligible patients were required to have a histological diagnosis of GCT and had to be judged as being incurable, i.e. with evidence of tumour progression/relapse after high-dose chemotherapy (HDCT) or absolute platinum-refractory tumours not being amenable to radical surgical resections. Patients had to be more than 16 years old, to have a Karnofsky performance status $\geqslant$60% and to be at least 3 weeks past HDCT or any major surgery. Additional inclusion criteria were the presence of bi-dimensionally measurable disease and/or elevated tumour markers as well as the lack of a history of thrombosis. Patients with a pre-existing peripheral neuropathy more than grade II according to the Common Toxicity Criteria (CTC) were also excluded from the study. No other concomitant chemotherapy, radiotherapy or experimental medications were allowed.

Evaluations at study entry included the following: patient history, a detailed physical and neurological examination, an assessment of the performance status, the documentation of all measurable disease by conventional X-ray, computed tomography (CT) or magnetic resonance tomography (MRT) scans, determinations of the serum levels of alpha-foetoprotein (AFP), of the beta subunit of human chorionic gonadotrophin (HCG) and of lactate dehydrogenase (LDH), as well as routine laboratory parameters such as serum creatinine, liver function tests and a complete blood count.

2.2. Treatment

Study treatment consisted of increasing oral doses of thalidomide. An absolute dose of 100 mg/d was given during the first week of treatment, 200 mg/d was administered during the second week and a dose of 400 mg/d was given during the subsequent weeks until tumour progression or unacceptable toxicities occurred. In the case of insufficient tumour response after 6–8 weeks, the thalidomide dosage could be escalated to a maximal dose of 600 mg/d. All patients were treated on an outpatient basis. Thalidomide was provided by the manufacturer (Grünenthal, Aachen, Germany).

2.3. Response criteria

Patients were assessed for response every 4 weeks by physical examination and determinations of serum tumour markers. More extensive diagnostic procedures (e.g. conventional X-rays, CT or MRT scans) were performed every 8 weeks. Standard criteria for complete remission (CR) and partial remission (PR) were used. In addition, patients without a radiological response, but a reduction of one-log of elevated HCG levels or a reduction of 50% or more in elevated AFP were classified as serological PR (4). Any patient with an increase in radiological manifestations of more than 25%, the appearance of any new lesions or any persistent increase in any tumour marker of 10% or more was considered as having progressive disease (PD), which prompted treatment with thalidomide to be stopped. Patients with disease not classified by any of the above-mentioned response criteria were classified as having stable disease (SD). Response criteria had to be present for at least 4 weeks.

2.4. Platinum sensitivity

Sensitivity to platinum was assessed and classified as reported previously.[8] Any disease was considered sensitive to platinum when at least SD was achieved for more than 4 weeks duration. Any disease was considered refractory to platinum when SD or better was achieved, but when there was evidence of tumour progression within 4 weeks of the last platinum-based treatment. Any disease was considered absolutely refractory to platinum when not even SD was achieved despite platinum-based chemotherapy.

Table 1 – Patient characteristics prior study entry (n = 15)

Patient characteristics	Median (range)	n	(%)
Age (years)	38 (25–47)		
Location of primary tumour			
Gonadal		13	87
Mediastinal		2	13
Sites of metastases			
Chest		12	80
Retroperitoneal		12	80
Liver		6	40
CNS		2	13
Other		3	20
Elevation of tumour markers			
AFP		9	60
β-HCG		4	27
LDH		3	20
No elevated markers		2	13
Cisplatin cycles (n)	6 (4–12)		
Failed pre-treatments with			
Cisplatin		15	100
Etoposide		15	100
Ifosfamide		15	100
Bleomycin		10	67
Paclitaxel		4	27
Failed treatment with HDCT		13	87
Late relapse >2 years		7	47
Cisplatin-sensitivity prior to thalidomide			
Sensitive		7	47
Refractory		3	20
Absolutely refractory		5	33

CNS, central nervous system; AFP, alpha-foetoprotein; HCG, human chorionic gonadotrophin; LDH, lactate dehydrogenase; HDCT, high-dose chemotherapy.

Table 2 – Characteristics of responding patients; (A) previous treatments; (B) characteristics at study entry and response

UPN	Age (years)	Primary tumour	Laterelapse	Time interval: initial diagnosis to study entry	Prior first-line and salvage chemotherapy	DDP cycles (*n*)	HDCT failed	Previous palliative treatments
(A)								
1	29	Gonadal	Yes	January 1995 to April 2002	DDP, VP-16, Ifo, Bleo	6	1 × CE	Oral VP-16
2	41	Gonadal	Yes	January 1987 to May 2002	DDP, VP-16, Ifo, Bleo	8	3 × CE	None
3	42	Gonadal	Yes	April 1989 to July 2002	DDP, VP-16, Ifo, Bleo, Vbl	8	None	Oral VP-16
5	25	Gonadal	No	March 2000 to July 2002	DDP, VP-16, Ifo, Bleo	6	1 × CEC	Oral VP-16
7	42	Gonadal	Yes	November 1997 to October 2002	DDP, VP-16, Ifo, Paclitaxel	9	3 × CE	Oral VP-16, gemcitabine + oxaliplatin
15	34	Gonadal	Yes	April 1989 to January 2003	DDP, VP-16, Ifo, Bleo, Vbl, Paclitaxel	12	2 × CE	Oral VP-16, gemcitabine + oxaliplatin

	DDP sensitivity prior thalidomide	Site of metastases	Tumour marker	Level of tumour marker	Thalidomide (mg/d)	Toxicities[a] (⩾II grade CTC)	Max. response	Response duration (months)	Survival status
(B)									
1	Abs. refractory	Chest	AFP	103, 434	400	Skin II	Serological PR	9	Dead
2	Sensitive	Retro	AFP	1618	300	Skin II	Serological PR	3	Dead
3	Abs. refractory	Chest, retro	AFP	1282	600	PNP III	Serological PR	12	Alive
5	Sensitive	Liver, retro	AFP	174	400	PNP II	SD	3	Dead
7	Sensitive	Chest	HCG	259	200	Sudden death	Serological PR	2	Dead
15	Sensitive	Chest, retro, liver	AFP	65	400	PNP II	Serological PR	4	Dead

UPN, unique patient number; HDCT, high-dose chemotherapy; DDP, cisplatin; VP-16, etoposide; Ifo, ifosfamide; Bleo, bleomycin; Vbl, vinblastine; CE, high-dose carboplatin/etoposide; CEC, high-dose carboplatin/etoposide/cyclophosphamide; retro, retroperitoneal; AFP, alpha foetoprotein; HCG, human chorionic gonadotrophin; LDH, lactate dehydrogenase; CTC, Common Toxicity Criteria; Max response, maximal response to thalidomide; PNP, polyneuropathy; PRm+, partial remission tumour marker positive; SD, stable disease.

a Other than lethargy and constipation.

2.5. Toxicity

Toxicity was assessed clinically every 4 weeks. Evaluations of toxicities were classified according to the common toxicity criteria of the National Cancer Institute (NCI-CTC).[9] Sensorimotor toxicity was considered to be grade II if minor impairment of daily activities were noted, to be grade III if objective loss of function occurred that interfered with daily activities, and to be grade IV when loss of function required supportive measures.

2.6. Statistical considerations

To detect a response rate of 20% or more with a β-error of 5%, a minimum of 15 patients had to included.

3. Results

3.1. Patient characteristics

Patient characteristics are shown in Table 1. All patients were intensively pre-treated and considered to be incurable of their disease. The majority of patients had failed HDCT as well as one or more palliative treatment regimens. Late relapses after 2 years since first-line treatment had occurred in 7/15 (47%) of patients studied.

3.2. Treatment responses

No CR or PR were achieved. However, serological PR was achieved in 5/15 (33%) patients. The median remission duration was 3 months (range 2–12 months), with 2 patients responding for 9 and 12 months, respectively (Table 2). One additional patient achieved SD for 3 months. All but 1 of the responding patients had abnormal levels of AFP and all responding patients had shown only slow tumour progression prior to thalidomide administration. Four of the responding patients had less than three tumour sites.

Responses seemed to be independent of platinum sensitivity, as 2/5 responders were considered to be absolute refractory to platinum prior the thalidomide administration. Patients with rapidly progressive tumours and all but one patient with tumour markers other than AFP did not benefit from thalidomide. Treatment with thalidomide was discontinued after 6–12 weeks in this latter group of patients.

At the time of last follow-up in January 2004, thalidomide was eventually discontinued in 14 patients because of PD and in 1 patient because of his unexpected death, respectively. In 4/15 patients with PD no further palliative treatment could be administered after failure of thalidomide due to advanced disease and poor performance status. The remaining 11/15 patients received further investigational palliative treatments with trofosfamide ($n = 5$), gemcitabine ± oxaliplatin ($n = 4$), temozolomide ($n = 1$) and capecitabine ($n = 1$).

Eventually all but 1 patient died from tumour progression. One patient is still alive with active disease. One patient experienced rapid mental deterioration and dyspnoea and died at home from an unknown cause while responding to thalidomide. Autopsy was refused by his relatives.

3.3. Toxicity

Thalidomide was administered at a median dose of 400 mg/d (range 200–600 mg). The toxic side-effects of this treatment were moderate. Lethargy and constipation NCI-CTC grade I or II were observed in all patients. The use of stool softeners helped to minimise constipation. The main toxicities were skin rash NCI-CTC grade II in 2 patients and peripheral sensory neuropathy NCI-CTC grade II and grade III, each in 2 patients. The latter patients all had pre-existing neuropathy that worsened about one grade during thalidomide treatment. the sudden death in 1 patient who received thalidomide at a dose of 200 mg/d could have been treatment related. No other severe toxicities occurred.

4. Discussion

To our knowledge this is the first study to evaluate the activity of thalidomide in patients with GCT.[5] All patients studied were considered incurable, having failed intensive first-line and salvage treatments, often including HDCT. Yet, thalidomide demonstrated activity with a reduction in serum tumour markers in the absence of radiological progression in 33% of patients, which compares favourably with other agents such as gemcitabine, oxaliplatin or paclitaxel that have been investigated in similar groups of intensively pre-treated patients.[2–4] Responses to thalidomide were rapid, usually within a few weeks of treatment and started to occur at doses as low as 200 mg/d. However, in 4 patients responses were seen only after escalation to doses between 400 and 600 mg. This might limit the use of thalidomide in patients with pre-existing neuropathies or poor renal function. Responders tended to have AFP as their main tumour marker, to have a low tumour burden and slowly progressive disease prior to treatment with thalidomide. With two absolute refractory patients responding, platinum sensitivity did not seem to predict for responses to thalidomide. Toxicities were manageable in most patients with lethargy, constipation and skin rashes as the most frequent side-effects. However, 4 patients (26%) showed clinically relevant worsening of their pre-existing neuropathy and 1 patient died possibly related to thalidomide administration.

The present study is clearly limited by the small number of patients. In particular, more experience is needed better to identify subgroups of patients who might profit most from treatment with thalidomide. As the dose of thalidomide was quickly escalated to 400 mg/d, we cannot exclude the possibility that lower doses of thalidomide might also be active if given over longer periods of time in patients with slowly progressing tumours. Still, our findings suggest that thalidomide has activity in intensively pre-treated GCT that may be independent of platinum sensitivity. Studies that further explore the use of thalidomide in germ-cell tumours are warranted.

Conflict of interest statement

None declared.

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