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Frequent good partial remissions from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma

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Summary. Twenty-three patients with advanced and heavily pretreated myeloma were treated with thalidomide. Starting dose was 200 mg/d, and 20 patients had dose escalations up to 400 ($n = 5$), 600 ($n = 12$) or 800 mg/d ($n = 3$), usually in divided doses. Nineteen patients were refractory to recent chemotherapy, and four had untreated relapse after prior intensive therapy. Ten out of 23 patients (43%) achieved partial response (PR; nine with refractory and one with relapsed disease), six patients had minor response or stabilization of the disease and four had disease progression. Another three patients died early from advanced myeloma at less than 3 weeks of thalidomide therapy. Of the 10 patients with PR, seven had a better response than after any prior therapy, despite vincristine–doxorubicin–dexamethasone (VAD)-based treatment in all but one and high-dose melphalan with autologous stem cell support in four. Time to achieve PR was rapid in patients receiving thalidomide in divided doses (median 31 d). Responses also included reduced bone marrow plasma cell infiltration and improved general status. Normalized polyclonal gammaglobulin levels were seen in four cases. Six out of 10 patients with PR remained in remission with a median time on treatment of 23 weeks (range 15–50 weeks). Sedation was common but usually tolerable, and some patients continued full- or part-time work. Four patients had skin problems, three patients had pneumonia, one hypothyrosis, one sinus bradycardia and one minor sensory neuropathy. Thalidomide may induce good partial remissions in advanced refractory myeloma with tolerable toxicity, and should be evaluated in other settings for myeloma patients. Divided thalidomide doses seem to reduce time to achieve remission and may improve response rate.

Keywords: myeloma, thalidomide, therapy, refractory, response.

Few drug types with documented effect as treatment for myeloma are currently available. Steroids and alkylating agents, mainly melphalan and cyclophosphamide, have significant and dose-related anti-tumour effects. In contrast, clinical benefit of anthracyclins have not been documented, but still they are frequently incorporated into combination chemotherapies (Barlogie *et al*, 1984). High-dose dexamethasone pulse-based therapy (Barlogie *et al*, 1984) followed by high-dose melphalan with autologous stem cell support (Barlogie *et al*, 1999) leads to a prolonged disease control with significant improvement in survival (Attal *et al*, 1996; Barlogie *et al*, 1997; Lenhoff *et al*, 2000). Still, the complete response rate is well below 50%, cure has not been documented, as progression-free survival is limited to a few years, and there is no plateau in the survival curves. However, recent studies suggest that allogeneic stem cell transplantation may improve response duration and outcome.

Thalidomide (α-(*N*-phthalimido)glutarimide; $C_{13}H_{10}N_2O_4$) is a drug that was used as a sedative in the 1960s, but that was withdrawn because of severe birth defects. It has a slow absorption after oral administration, a plasma half-life of about 6 h, and is degraded by non-enzymatic hydrolysis. It has immunomodulatory effects with a down-regulation of tumour necrosis factor α (Shannon *et al*, 1997; Haslett *et al*, 1998); up-regulation of adhesion molecules (Geitz *et al*,

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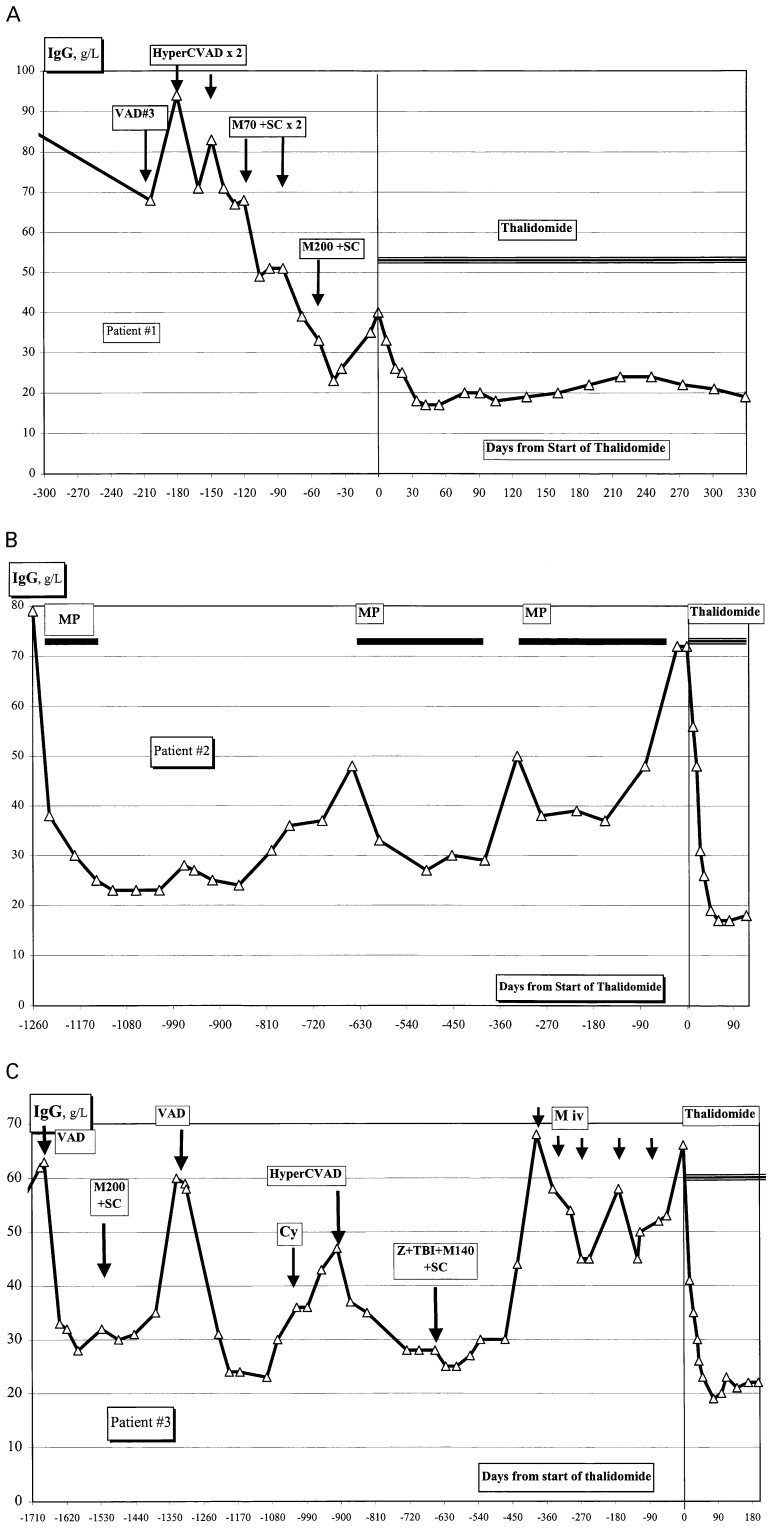

Fig 1. Serum IgG M protein levels for patients 1–3 (A–C respectively) before and during thalidomide treatment. Time points for previous therapies are indicated by arrows. MP, melphalan 0·25 mg/kg and prednisone 2 mg/kg for 4 d every 6-weeks; VAD and HyperCVAD, given according to Barlogie *et al* (1984) and Dimopoulos *et al* (1996) respectively; SC, autologous stem cell support; Cy, cyclophosphamide 2 g/m^2; Z + TBI + M, high-dose idarubicin (42 mg/m^2), total body irradiation (12 Gy) and melphalan 140 mg/m^2; M iv, melphalan 30–70 mg intravenously; M70, melphalan 70 mg/m^2; M200, melphalan 200 mg/m^2.

1996) and also antiangiogenetic properties (Bauer *et al*, 1998; Or *et al*, 1998; Berenson *et al*, 1999; Gasparini, 1999). It has been used as therapy for erythema nodosum in leprosy, for Behcet's disease, for HIV-related cachexia and recurrent aphthous stomatitis (Jacobsen *et al*, 1997) and also for graft-versus-host disease after allogeneic bone marrow transplantation (Vogelsang *et al*, 1992).

Myeloma is commonly accompanied by an increased microvessel density of the bone marrow, which is considered to be an adverse prognostic factor (Vacca *et al*, 1994;

Berenson *et al*, 1999). Such an increased vascularization may persist after high-dose therapy (Rajkumar *et al*, 1999) and contribute to relapse.

Recently, positive treatment results with thalidomide given to 84 patients with advanced myeloma were reported as 21 patients (25%) achieved at least partial response from thalidomide in doses ranging from 200 to 800 mg per day, always given as a single dose in the evening (Singhal *et al*, 1999).

We report here the Swedish experience from advanced myeloma treated with thalidomide mostly given in divided daily doses.

MATERIALS AND METHODS

Patients. Twenty-three patients with previously treated advanced myeloma from five Swedish centres are reported. There were 16 men and seven women, and the median age was 61·1 years (range 44–78). Myeloma subtype was IgG in 14 cases, IgA in five and only Bence-Jones proteinuria in four. Light chains were kappa in nine, lambda in two and data were unavailable in 12. All but one (patient 2; Fig 1) had had multiple prior therapies, including vincristine–doxorubicin–dexamethasone (VAD)-like therapies (Barlogie *et al*, 1984), and 10 had undergone high-dose melphalan with autologous stem cell support. The disease duration from start of initial treatment was 44 months (range 7–137). At inclusion, 19 patients had disease refractory to ongoing treatment, whereas four had untested relapse after prior intensive therapy. The median plasma cell infiltration in the bone marrow was 38% ($n = 16$, range 6–90%), and serum beta-2-microglobulin 4·1 mg/l ($n = 11$, range 1·7–5·8). The median M-protein level for IgG patients was 49 g/l (range 21–72 g/l) and for IgA patients it was 24 g/l (range 13–44 g/l).

Drug therapy. Thalidomide tablets (Grünenthal, Aachen, Germany) were given orally, following individual approval from the Swedish Medical Drug Agency. The starting dose was initially 200 mg twice daily, but as some patients became very sedated from the first dose subsequent patients started on 100 mg twice daily. Dose escalation to 200 mg twice daily was performed within 1 week, and subsequently, according to tolerance, to 300 or 400 mg twice daily. Seven patients in one centre had one daily dose of up to 800 mg thalidomide given in the evening. The dose escalation strategy resulted in a maximum thalidomide dose of 800 mg/d in three patients, 600 mg/d in 12 patients and 400 mg/d in five; three patients in poor condition who had an early death did not have dose escalation. Therapy was continued in individual dosing according to response and tolerance until prohibitive toxicity, progression, death or allogeneic stem cell transplantation. Response was evaluated according to the EBMT/IBMTR/ABMTR guidelines (Bladé *et al*, 1998).

RESULTS

Patients with partial response

Ten patients (43%) had partial response (PR) (Bladé *et al*, 1998) (Tables I and II), two of them had maximum doses of 800 mg thalidomide/d, seven had 600 mg/d and two had 400 mg/d. Seven of these patients had a better response to thalidomide than to any previous therapy, including high-dose melphalan with stem cell support in four and VAD-like treatment in all but one (patient 2). PR was achieved in 8/16 (50%) patients having thalidomide in divided doses, compared with 2/7 (29%) of those who had single daily doses (including patients with early deaths). The clinical courses for three of these patients (1–3) are illustrated in Fig 1. One patient, who did not tolerate higher doses of thalidomide because of somnolence and dizziness, seemed to have a direct correlation between thalidomide dose and M-protein level (patient 4; Fig 2). Another patient (9) with side-effects due to thalidomide had a rapid disease progression after cessation of thalidomide. One patient with PR had progression on 600 mg/d thalidomide after 31 weeks (patient 8), whereas other patients have had continuing paraprotein response to date or until allogeneic transplantation or death (Table I).

Time to achieve partial response was rapid; among eight patients who had PR to thalidomide in divided doses, the median time to PR was 31 d (range 28–81 d), whereas for two patients who had PR to single-dose daily therapy (patients 7 and 8) the time to PR was 70 d in one and 116 d in the other patient. Responding patients rapidly showed evidence of responsiveness through declining paraprotein levels after only 1 week of therapy (Fig 1). The serum M-protein levels before and during thalidomide therapy for all individual patients (except for those with early death) are shown in Fig 3. Improvements of anaemia and skeletal pain was usually slower, although responding patients had a

Table I. Response to thalidomide according to thalidomide dosing (number of patients).

	Refractory	Relapsed	
	Divided/single dose	Divided/single dose	Total
Partial response	7/2	1/0	10
Stable disease/minor response	1/2	2/1	6
Progression	3/1	0/0	4
Early death	2/1	0/0	3
Total	13/6	3/1	23

Table II. Characteristics of patients with partial response to thalidomide.

Patient no. (age/sex)	Ig isotype/ stage	Disease duration (months)	Therapy prior to thalidomide	Refractory/ relapse to prior therapy	Highest dose of thalidomide	Thalidomide response duration (weeks)	Outcome
1 (57/M)	IgG-kappa/IIIA	10	VAD × 3, HyperCVAD × 2, M70 + SC × 2, M200 + SC	Refractory	400 mg × 2	48	Continuing response
2 (72/M)	IgG-lambda/IIIA	137	MP × 18	Refractory	200 mg × 2	20	Dead, obstructive lung disease
3 (52/M)	IgG/IIIA	55	VAD × 3, M200 + SC, IFN VAD × 2, HDCy, HyperCVAD ZTBIM + SC, M iv × 5	Refractory	300 mg × 2	32	Continuing response
4 (56/M)	IgA-kappa/IIIA	51	VAD × 3, M200 + SC, IFN VAD × 5, VBAP, VAD × 4, Dex	Refractory	200 mg × 2	35	Dose-related response
5 (54/M)	IgG-kappa/IIIA	70	VAD × 3, M200 + SC IFN, VADx2, RT	Refractory	300 mg × 2	24	Allotransplant
6 (44/F)	BJ-kappa/IIIA	28	VAD × 3, M200 + SC, IFN	Relapse	200 mg × 3	20	Allotransplant
7 (54/F)	IgG/IIIB	45	VAD × 3, VACP × 5	Refractory	600 mg × 1	50	Continuing response
8 (64/F)	IgG/IIIA	71	CyD + IFN × 3, VACP × 24	Refractory	600 mg × 1	31	Progression on treatment
9 (68/M)	IgG-kappa/IIIA	34	MP × 5, Z × 3, VAD × 5	Refractory	400 mg × 2	15	Progression off treatment
10 (68/F)	IgA/IIIA	17	CyD × 3, M200 + SC IFN, RT, MP × 2	Refractory	300 mg × 2	16	Dead, bone marrow failure

IFN, interferon alpha; RT, radiotherapy, CyD, cyclophosphamide + dexamethasone; VBAP, vinblastine, BCNU, doxorubicin, prednisone; VACP, etoposide, doxorubicin, cyclophosphamide, prednisone; Z, idarubicin orally. For further abbreviations, see legend to Fig 1.

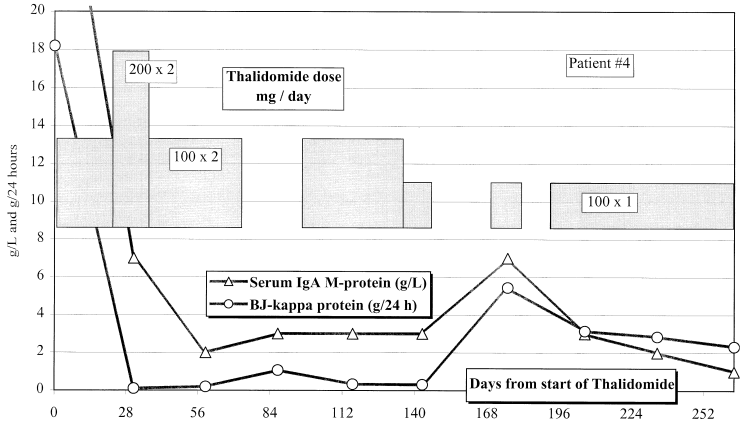

Fig 2. Serum IgA M-protein level and Bence-Jones kappa proteinuria excreted per 24 h in relation to thalidomide dose in patient 4, who experienced dose-related dizziness and vertigo.

significant subsequent improvement of blood counts, symptoms and performance status. Significant improvement of cytopenia was seen in patients with minor response. Haemoglobin levels and platelet counts from start of thalidomide therapy for selected patients with PR or minor response are shown in Fig 4.

Responding patients had a decrease in bone marrow plasma cell infiltration to usually below 10%, and serum beta-2-microglobulin levels also improved in all five patients with follow-up samples available.

Four responding patients had improvement of their polyclonal gammaglobulin levels (patients 2, 5, 6 and 10). Polyclonal IgG levels were normalized in one patient with IgG myeloma (from less than 1 up to 6 g/l; patient 5), one with IgA myeloma (4·9 up to 9·8 g/l; patient 10) and one with Bence-Jones myeloma (5·2 up to 9·2 g/l; patient 6), and one patient with IgG myeloma improved his IgA level from 0·13 g/l up to 0·93 g/l (patient 2).

One patient (10), who had a prompt and early reduction of her IgA paraprotein during the first month of thalidomide, developed a progressive paraparesis due to spinal plasmacytoma that was diagnosed by magnetic resonance tomography and treated with surgery followed by radiotherapy, leading to a partial clinical response. She subsequently developed bone marrow failure 3 months after the start of thalidomide and died.

There was no clear-cut correlation between myeloma isotype and response. Patients achieving PR were younger (median age 56·5 years vs. 63 years for others), possibly reflecting a better ability to accept thalidomide toxicity. Nine of 16 (56%) patients refractory to ongoing treatment had partial response compared with one of four patients given thalidomide as a result of progression off therapy (Table I).

Patients with less than partial response

Among three patients with relapse, minor responses were achieved from thalidomide in two, and a significant stabilization of the disease in one case. Two of them, both with prior autotransplantation, subsequently received oral melphalan and prednisone, and had a minor reduction of their M-protein levels at the cost of deteriorating blood counts. Three patients refractory to previous therapy had minor responses, and another had a short clinical improvement followed by disease progression and death. Three patients had continuing myeloma progression, in one of them thalidomide was discontinued early because of skin toxicity.

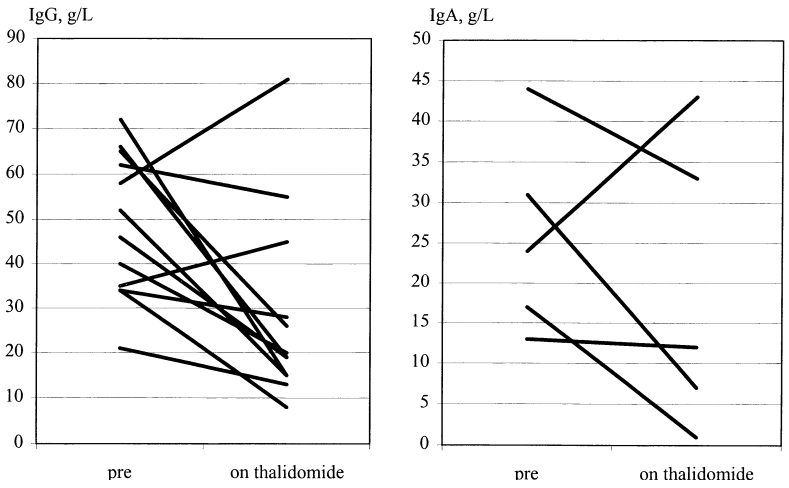

Fig 3. Serum M-protein before and during thalidomide treatment for patients with IgG and IgA myelomas.

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