THALIDOMIDE IN MULTIPLE MYELOMA: CURRENT STATUS AND FUTURE PROSPECTS

Guideline

Thalidomide was introduced in Europe during the 1950s as a sedative agent and was found to be particularly effective at alleviating the symptoms of morning sickness. As is widely known, it was subsequently withdrawn in 1961 after its teratogenic properties were recognized, in particular, its ability to cause phocomelia. Damage to the fetus occurs early in pregnancy (from d 28–42 post conception) and the limb bud abnormalities are thought to be due to inhibition of normal vessel formation. Since that time, thalidomide’s immunomodulatory effects have been recognized and it has been used, in a cautious and restricted manner, in the treatment of such disparate disorders as Behcet’s disease, erythema nodosum leprosum, human immunodeficiency virus-associated oral ulceration and chronic graft-versus-host disease. More recently, the drug has been tested in a variety of solid and haematological malignancies, and has shown remarkable efficacy in patients with advanced multiple myeloma. Indeed, the use of thalidomide is arguably the most significant advance in the treatment of myeloma following treatment with thalidomide has proven anti-angiogenic activity as it can inhibit angiogenesis induced by basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) in inhibit angiogenesis induced by basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) in patients with advanced multiple myeloma.

MECHANISMS OF ACTION: ANTI-ANGIOGENESIS

Many tumours require new vessel formation in order to support their continued growth (Folkman, 1974; Holmgren et al, 1995) and various lines of evidence suggest that neoangiogenesis is also important in the pathogenesis of myeloma. Myeloma bone marrow shows increased microvessularity and its density correlates with the clinical aggressiveness of plasma cell neoplasms (Vacca et al, 1994). Furthermore, the density of bone marrow vascularity has important prognostic implications such that patients with extensive vascularity have reduced overall survival (OS) (24 months) compared with patients with less extensive vascularity (53 months) (Rajkumar et al, 2000a). In addition, myeloma cells secrete a variety of angiogenic factors and their level of secretion is again correlated with activity of disease (Bellamy et al, 1999; Vacca et al, 1999). Thalidomide has proven anti-angiogenic activity as it can inhibit angiogenesis induced by basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) (D’Amato et al, 1994), although there was no significant reduction in microvascular density or in the plasma levels of VEGF or bFGF following treatment with thalidomide (Singhal et al, 1999; Neben et al, 2001). The exact mechanism whereby this effect is achieved remains uncertain, although it is known that thalidomide analogues impair VEGF-induced mitogen-activated protein kinase (MAPK) signalling pathways (Lentzsch et al, 2000). Indeed, thalidomide was first tested in myeloma because of its known anti-angiogenic activity.

OTHER POTENTIAL MECHANISMS OF ACTION

Although thalidomide is known to interfere with angiogenesis, it possesses other potential mechanisms of action. Furthermore, a number of thalidomide analogues have been developed that possess distinct spectra of biological activities. The two major classes of analogue are known as ‘selected cytokine inhibitory drugs’ or SelCIDs and ‘immunomodulatory drugs’ or IMiDs. The former are phosphodiesterase type 4 inhibitors and result primarily in reduced tumour necrosis factor α (TNFα) production, whereas the latter do not inhibit phosphodiesterase type 4 but stimulate T-cell proliferation and the production of interleukin 2 (IL-2) and interferon-γ (IFN-γ) (Corral et al, 1999).

Thalidomide can directly inhibit the growth and survival of myeloma cells, perhaps by oxidative damage to DNA mediated by free radicals (Furman et al, 1999). The drug can certainly directly induce apoptosis even in drug-resistant myeloma cells (Hideshima et al, 2000). IMiD 1 induces apoptosis in myeloma cells in a similar fashion to dexamethasone by activating related adhesion focal tyrosine kinase (RAFTK) (Hideshima et al, 2000). Both dexamethasone and IMiD 1-induced apoptosis are abrogated by exogeneous IL-6 (Hideshima et al, 2000). In addition, thalidomide modulates cell adhesion molecule expression, so it may well interfere with the mutually stimulatory interactions between myeloma cells and the bone marrow microenvironment (Geitz et al, 1996). Importantly, the drug and its analogues also interfere with TNFα production (Moreira et al, 1993; Turk et al, 1996; Corral et al, 1999) and with DNA binding of nuclear factor-kB (NF-kB), so abrogating normal inflammatory cytokine production (Pavvandi et al, 2000). Finally, thalidomide has direct stimulatory effects on both T and natural killer (NK) cells (Haslett et al, 1998; Davies et al, 2001).

It seems probable that some or all of these mechanisms of action are relevant to the efficacy of thalidomide and its analogues in myeloma. Further clarification of the precise effects of thalidomide and similar agents is likely to be provided by analysis of the differential effects of thalidomide and its analogues.

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THALIDOMIDE AS A SINGLE AGENT FOR THE TREATMENT OF MYELOMA

Whatever its exact mechanism of action, thalidomide has impressive activity in myeloma, as first reported by Singhal et al (1999). In this pivotal study, 84 patients were treated with thalidomide at a starting dose of 200 mg/d, increasing in 200 mg increments every 2 weeks to a maximum dose of 800 mg/d. All patients had progressive disease and over 90% had received at least one high-dose procedure. Two thirds of the patients tolerated 600 mg/d but only half were able to take the maximum 800 mg dose. The total response rate was 32%, as defined by a fall in paraprotein level of at least 25%. Responses were associated with a reduction in bone marrow (BM) infiltration by malignant plasma cells and increases in haemoglobin levels. However, there was no clear correlation between responses and any reduction in BM microvascularity. In responders, a reduction in paraprotein level (> 25%) was achieved within 2 months in 78% of patients. Response rates were inversely correlated with the plasma cell labelling index (PCLI). For patients with a PCLI < 0.2% the response rate was 48%, whereas only 9% of those with a PCLI > 0.2% responded. Approximately one-third of the patients experienced side-effects, mainly somnolence, constipation and fatigue. These adverse events were classified as World Health Organization Grade 3–4 in < 10% of cases and were related to the dose taken. After 12 months of therapy, 44% of the patients had shown evidence of progression. The 12 month event-free survival (EFS) was 22% and the 12 month OS was 58%.

This report has been updated (Barlogie et al, 2001a), at which time 169 patients had been treated, with an overall response rate of 36%. Responses were more frequent in patients with a low PCLI and normal cytogenetics. Overall, the 2 year EFS and OS were 20% and 48%, respectively, with superior outcomes for those patients who actually responded to thalidomide (EFS 34% and OS 69%). However, 62% of patients showed evidence of disease progression and were withdrawn from the study. Thromboembolic events occurred in less than 5% of patients. Similar findings in smaller series of patients have been reported by others (Juliusson et al, 2000; Grosbois et al, 2001; Oakervee et al, 2001; Rajkumar et al, 2001a). Overall, approximately 30–45% of patients with relapsed or refractory disease have achieved a partial response in these studies, so confirming the activity of thalidomide as a single agent in advanced myeloma (see Table I).

The optimal dose of thalidomide has yet to be defined. Barlogie et al (2001a) have suggested that there is evidence of a dose–response effect with higher response rates being observed in those patients who receive more than 42 g of thalidomide within the first 3 months (54% vs 21% response rate, P = 0.001). In contrast, other investigators have observed similar response rates with doses varying from 50 to 200 mg/d (Durie & Stepan, 2001; Wechalekar et al, 2001). Similarly, when utilizing an escalating dose regimen, responses are usually first observed when patients are taking only 200 mg/d (Oakervee et al, 2001). Therefore, the optimal thalidomide dose remains uncertain and this issue can only be resolved by appropriate prospective clinical trials.

Thalidomide has been used alone in untreated, asymptomatic patients (dose 100–400 mg/d) with a response rate of 36% and a median duration of response of greater than 12 months (Weber et al, unpublished observations, Eighth International Myeloma Workshop, 2001) with other groups reporting similar results (Rajkumar et al, 2001b).

Table I.
(A) Response to thalidomide alone in relapsed/refractory disease.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>RR (&gt; MR)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>84</td>
<td>32%</td>
<td>12-months OS, 58%</td>
</tr>
<tr>
<td>169</td>
<td>36%</td>
<td>24-months OS, 48%</td>
</tr>
<tr>
<td>23</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>31%</td>
<td>&gt; PR only reported</td>
</tr>
<tr>
<td>32</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>31.7%</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>44%</td>
<td>Low dose (50–200 mg thal used)</td>
</tr>
</tbody>
</table>

(B) Response to thalidomide alone in untreated, asymptomatic disease.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>RR (PR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>36%</td>
</tr>
<tr>
<td>16</td>
<td>38%</td>
</tr>
</tbody>
</table>

RR, response rate; OS, overall survival; PR, partial response (> 50% reduction in paraprotein); MR, minor response (> 25% reduction in paraprotein).
THALIDOMIDE ANALOGUES

Certain of the thalidomide analogues demonstrate enhanced \textit{in vitro} activities that might predict superior clinical antitumour efficacy. In addition, these analogues do not have the teratogenic effects of thalidomide and it is also hoped that they will have a better side-effect profile than the parent drug. IMiD 3 (CC-5013, Celgene Corporation, Warren, NJ, USA) is among the most promising analogues \textit{in vitro} and displays significantly increased potency in inhibiting TNF-\(\alpha\) production, following lipopolysaccharide stimulation of peripheral blood mononuclear cells (PBMC). Likewise, CC5013 is 50–2000 times more active than thalidomide at stimulating T-cell proliferation and 50–100 times more active in augmenting the production of IL-2 and IFN-\(\gamma\) following T-cell receptor (TCR) ligation of PBMC and T cells respectively (Corral \textit{et al}, 1999). Furthermore, the IMiDs display a greater ability than thalidomide in inhibiting myeloma cell DNA synthesis \textit{in vitro} (Hideshima \textit{et al}, 2000).

For all these reasons, CC5013 and similar compounds (e.g. CC4047) are being investigated in early-phase clinical studies. Two phase I, dose-escalating studies have recently been reported (Richardson \textit{et al}, 2001; Zangari \textit{et al}, 2001a). Somnolence, constipation and neuropathy were not observed, although myelosuppression appears to be a problem and a single case of thromboembolism occurred. Although these are not primarily efficacy studies, it is encouraging to note that 12/19 evaluable patients in the Dana Farber study (Richardson \textit{et al}, 2001) showed at least a 25% paraprotein reduction. On the basis of these results, phase II/III trials are being designed.

THALIDOMIDE PLUS DEXAMETHASONE

The activity of thalidomide as a single agent in advanced myeloma, along with \textit{in vitro} evidence of synergistic effects, has prompted investigation of the combination of thalidomide with dexamethasone. In one such study from the MD Anderson Cancer Center, 44 evaluable patients with relapsed or refractory disease were initially treated with thalidomide alone and 25% achieved a partial response (PR) (Weber \textit{et al}, 1999). Thalidomide was started at 200 mg/d, increasing every 2 weeks to a maximum of 800 mg/d. Of note, all responses were observed with doses less than or equal to 400 mg/d. Of the 26 non-responders, approximately 35% went on to show a response to the combination of thalidomide with pulsed dexamethasone, suggesting synergy between these two agents in the clinical setting (Table IIA). Two similar small studies have been reported, although there were differences in the thalidomide dose (100 mg rising to 600 mg and 100 mg at a fixed dose respectively) and in the exact pulsed dexamethasone regimen (Palumbo \textit{et al}, 2001; Tosi \textit{et al}, 2001) (results summarized in Table II). PR rates of 26% and 48% were observed respectively. In the latter study, thalidomide/dexamethasone-treated patients were compared with pair-mates treated with melphalan and prednisolone. Similar response rates were observed but with reduced toxicity. In none of these three studies was an excess of thromboembolic events reported.

These results in patients with advanced myeloma have prompted the investigation of this combination in newly diagnosed patients (Table IIB). A major potential advantage of this regimen is that it obviates the need for a long-term central venous catheter with its associated risks of infection and line-related thrombosis. Rajkumar \textit{et al} (2001c) from the Mayo Clinic have reported on the first 50 patients with active myeloma treated in this manner. Thalidomide was initially escalated up to 800 mg/d but after the occurrence of unexpected, severe skin rashes in two of the first seven treated patients, the dose was fixed at 200 mg. The observed PR rate was 64%, which was comparable to VAD (vincristine, adriamycin, dexamethasone)-like regimens. Venous thromboembolism (VTE) was seen in 10% of patients.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>RR (PR)</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>35%</td>
<td>All refractory to thal alone</td>
<td>Weber \textit{et al} (1999)</td>
</tr>
<tr>
<td>27</td>
<td>26%</td>
<td></td>
<td>Tosi \textit{et al} (2001)</td>
</tr>
<tr>
<td>44</td>
<td>48%</td>
<td></td>
<td>Palumbo \textit{et al} (2001)</td>
</tr>
<tr>
<td>7</td>
<td>43%</td>
<td>Failed thal alone</td>
<td>Durie &amp; Stepan (2001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>RR (PR)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>64%</td>
<td>Rajkumar \textit{et al} (2001c)</td>
</tr>
<tr>
<td>16</td>
<td>69%</td>
<td>unpublished observations</td>
</tr>
</tbody>
</table>

RR, response rate; PR, partial response > 50% reduction in paraprotein.

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patients, a significantly higher incidence than that generally observed with this regimen in patients with relapsed disease. This phase II study has led the Eastern Cooperative Oncology Group (ECOG) to initiate a randomized study for patients with newly diagnosed myeloma in which patients receive pulsed dexamethasone with or without thalidomide at 200 mg/d with the aim of proceeding to high-dose melphalan and stem cell rescue after 4 months of induction therapy.

**THALIDOMIDE PLUS CHEMOTHERAPY**

There have been encouraging reports concerning the efficacy of thalidomide combined with dexamethasone and chemotherapy. Twelve of 14 (86%) patients with advanced myeloma achieved a PR to the combination of hyperfractionated cyclophosphamide, dexamethasone and thalidomide (‘Hyper-CDT’) (Kropff et al, 2000). Responding patients were maintained on pulsed dexamethasone and thalidomide with no progression observed after a median of 7 months. In a second study, 42 patients with advanced disease were treated with T-CED (thalidomide, cyclophosphamide, etoposide and dexamethasone; TCD, pulsed thalidomide, cyclophosphamide and dexamethasone; TVAD, thalidomide, vincristine, adriamycin and dexamethasone; MPT, melphalan, prednisolone and dexamethasone; BLT-D, clarythromycin (biaxin), low-dose thalidomide and dexamethasone).

Further cycles of DT-PACE. The purpose of this study was to determine whether further DT-PACE could substitute for tandem autografts in DT-PACE-sensitive disease. The 2 year EFS and OS in the tandem autograft and further DT-PACE groups were 63%/81% and 65%/79% respectively. The number of thromboembolic events was not reported as being unexpectedly high. Although these outcomes were no different, it is difficult to draw firm conclusions from this study as 58% of patients in the further DT-PACE arm crossed over to the tandem autograft arm because of failure to achieve predefined levels of response. Furthermore, only 40% of eligible patients were actually randomized. Nevertheless, the investigators felt able to conclude that DT-PACE is an excellent induction regimen for previously treated myeloma patients but that high-dose therapy is still required for durable disease control.

These impressive results observed in patients with advanced disease have encouraged the initiation of studies examining the combination of thalidomide with conventional chemotherapy in newly diagnosed patients with myeloma. The largest such study again is being conducted at The University of Arkansas for Medical Sciences. Patients are treated with sequential chemotherapy and tandem autografts (Total Therapy II) with or without thalidomide (Barlogie et al, 2001b). This study is ongoing and results are awaited with interest. Two feasibility studies are being conducted by the United Kingdom Myeloma forum (UKMF), concerning the combination of thalidomide with chemotherapy. Patients for whom high-dose melphalan is felt to be appropriate are eligible for the T-VAD protocol (thalidomide at 200–400 mg with VAD). Because of early concerns that prior exposure to thalidomide might interfere with stem cell mobilization (Munshi et al, 1999), patients are treated initially with a single cycle of VAD chemotherapy prior to a first ‘back-up’ stem cell harvest. They then receive concurrent VAD and thalidomide to maximum response, a second stem cell harvest, and consolidation with high-dose melphalan and stem cell rescue utilizing the second harvest. Of the 12 patients so treated, 11 successfully mobilized stem

### Table III. Response rates to thalidomide and chemotherapy.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of patients</th>
<th>RR (PR)</th>
<th>Advanced/de novo disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HyperCDT</td>
<td>14</td>
<td>86%</td>
<td>Advanced</td>
<td>Kropff et al (2000)</td>
</tr>
<tr>
<td>T-CED</td>
<td>42</td>
<td>78%</td>
<td>Advanced</td>
<td>Moehler et al (2000)</td>
</tr>
<tr>
<td>TCD</td>
<td>24</td>
<td>50%</td>
<td>Previously treated</td>
<td>Dimopoulos et al (2001)</td>
</tr>
<tr>
<td>TVAD</td>
<td>12</td>
<td>100%</td>
<td>11/12 de novo patients; 1 advanced</td>
<td>Oakervvee et al (2002a)</td>
</tr>
<tr>
<td>MPT</td>
<td>13</td>
<td>38%</td>
<td>Newly diagnosed</td>
<td>Oakervvee et al (2002b)</td>
</tr>
<tr>
<td>MPT</td>
<td>9</td>
<td>44%</td>
<td>Relapsed</td>
<td>Oakervvee et al (2002b)</td>
</tr>
<tr>
<td>BLT-D</td>
<td>55 (40 evaluable)</td>
<td>93%</td>
<td>46 advanced disease</td>
<td>Coleman et al, unpublished observations, Eighth International Myeloma Workshop (2001)</td>
</tr>
</tbody>
</table>

RR, response rate; PR, partial response > 50% reduction in paraprotein; HYPER-CDT, cyclophosphamide, dexamethasone and thalidomide; T-CED, thalidomide, cyclophosphamide, etoposide and dexamethasone; TCD, pulsed thalidomide, cyclophosphamide and dexamethasone; TVAD, thalidomide, vincristine, adriamycin and dexamethasone; MPT, melphalan, prednisolone and dexamethasone; BLT-D, clarythromycin (biaxin), low-dose thalidomide and dexamethasone.
cells at the first and 10/11 at the second attempt (Oakervee et al, 2002a). The patient who failed initial mobilization still had high disease bulk at the time, whereas the single patient who failed to mobilize for a second time had been previously treated with oral melphalan and C-VAMP (cyclophosphamide, vincristine, adriamycin, methyl prednisolone). Therefore, it appears that T-VAD does not interfere with subsequent stem cell mobilization. Of note, 12/12 patients achieved at least a PR. Four thrombotic events have been observed; three line-related and one pulmonary embolism (PE).

A second UKMF study is examining the combination of melphalan and prednisolone with thalidomide (MPT) in patients for whom high-dose therapy is not felt to be appropriate. Twenty-two patients have been treated (13 untreated, nine previously treated) with an overall 41% PR rate. However, 3/13 previously untreated patients developed deep vein thrombosis (DVT)/PE (Oakervee et al., 2002b). This was felt to be more than expected and the study was therefore closed prior to the accrual of 25 planned patients.

Another approach in advanced disease has been to combine low-dose thalidomide (50–200 mg) with dexamethasone and clarithromycin (Biaxin) (BLT-D). Fifty-five patients (49 with myeloma) were treated on this regimen (Coleman et al., unpublished observations, Eighth International Myeloma Workshop, 2001). Of 40 evaluable patients, 93% had at least a PR and 13% achieved complete responses.

VTE WITH THALIDOMIDE

The use of thalidomide in a variety of non-malignant conditions has generally been associated with a low but definite risk of VTE, although neuropathy continued to be considered as the most serious potential adverse event. However, as experience has been gained with its use in myeloma, VTE has emerged as the single most important complication of thalidomide therapy in this setting.

Although VTE has been observed with the use of thalidomide as a single agent in the treatment of patients with advanced myeloma, VTE frequency has generally been less than 5%. Similarly, an excessive rate of VTE has not been reported with the use of thalidomide in combination with a variety of chemotherapies in patients with relapsed myeloma. However, an unexpectedly high risk of VTE has been observed when thalidomide is combined with chemotherapy for newly diagnosed patients with myeloma. Rajkumar et al (2001c) reported a 10% incidence of VTE when using the combination of thalidomide with dexamethasone as initial therapy, which was higher than that observed when the same regimen was used in relapsed or refractory patients. This is roughly equivalent to the VTE rate seen with conventional VAD-like regimens. Of more concern is a report by Osman et al (2001) of a VTE incidence of 4/15 when the ‘TAD’ regimen was used as induction therapy for newly diagnosed patients. This comprised thalidomide (100 mg rising to 200 mg/d), peripheral bolus adriamycin and pulsed dexamethasone. Of the four VTE events, all were proximal lower limb DVTs: two were bilateral and all occurred early in the treatment schedule (R. Comenzo, personal communication). These findings led the investigators to terminate this phase II study early.

Important corroborative evidence has come from investigators at The University of Arkansas for Medical Sciences. They compared the incidence of VTE among patients randomized to the addition of thalidomide (400 mg) with chemotherapy in their ‘Total Therapy II’ study (Zangari et al, 2001b). Among 100 patients so randomized, the incidence of VTE was 4% in the no thalidomide arm and 28% in the thalidomide arm (P = 0.002). All episodes of VTE occurred within the first three cycles of chemotherapy. All 100 patients had central venous catheters (CVC) in place. In the 50 patients not receiving thalidomide, VTE was CVC related in one case and distant in another case. In contrast, for the 50 patients receiving thalidomide, VTE was CVC related in three cases and distant in 11. Therefore, it is clear that the major increase in risk is for distant, non-CVC-related VTE. This suggests that the combination of thalidomide with chemotherapy in newly diagnosed patients with myeloma results in a systemic prothrombotic state.

To date, no identifiable prothrombotic laboratory abnormality has been found to be predictive of VTE in this group of patients (Zangari et al, 2000). In particular, neither the levels of protein C, protein S and anti-thrombin III nor the incidence of anti-phospholipid antibodies, activated protein C resistance (APCR), factor V Leiden and prothrombin gene promoter mutation have been found to correlate with increased risk of VTE in patients receiving thalidomide (Zangari et al, 2001c), although only small numbers of patients have been studied to date. Among similar groups of patients being treated with thalidomide plus chemotherapy, the addition of adriamycin to the regimen resulted in an increased VTE rate (Zangari et al, 2001c). In an analysis of the Federal Drug Administration’s passive reporting system, varying rates of VTE were found when thalidomide was used in different combinations in patients with a variety of cancers. VTE rates were 4–6%, 15% and 30–90%, respectively, when thalidomide was used alone, in combination with dexamethasone and with chemotherapy (Bennett et al, 2001) (see Table IV).

It can be concluded that the use of thalidomide concurrently with chemotherapy in patients with newly diagnosed myeloma carries a significant risk of VTE. This risk appears to be considerably greater than that associated with the use of thalidomide as a single agent or when combined with chemotherapy in patients with relapsed disease. In addition, the major risk of VTE occurs early on in treatment when the tumour load is maximal. It seems that it is the combination of thalidomide, chemotherapy and large disease bulk that is particularly prothrombotic in myeloma. In this regard, it is of potential interest that only 1/12 patients treated to date on the UKMF T-VAD protocol has developed ‘distal’ VTE (Oakervee et al, 2002a). On this protocol, patients are treated with an initial cycle of VAD with a subsequent cyclophosphamide-primed stem cell harvest prior to commencing T-VAD. It is possible that the level of tumour reduction, resulting from this initial chemotherapy, reduces...
the risk of VTE when thalidomide is subsequently initiated. Clearly, a larger number of patients need to be treated with T-VAD in order to draw any firm conclusions.

Patients with myeloma frequently have multiple conventional risk factors for VTE such as immobility, dehydration, increased plasma viscosity, intercurrent infection and acquired APCR (Zangari et al., 2001c). Indeed, in an analysis of 69 patients, acquired APCR was seen in 23% of patients and VTE was more common in this group of patients than in those without resistance (36% vs 13%, \( P = 0.04 \)). Acquired APCR is influenced by a large number of factors, including the acute-phase response (Clark & Walker, 2001), which are commonly found in myeloma patients. All such patients should be considered for appropriate VTE prophylaxis and preliminary observations from Barlogie’s group suggest that prophylactic low-dose warfarin is effective in reducing the VTE rate to baseline in patients receiving thalidomide simultaneously with chemotherapy. Furthermore, such combination treatment can be safely continued in patients with VTE once therapeutic anticoagulation has been established. Prospective studies will be needed to clarify what is the most effective method of, and the groups of patients who will benefit most from, VTE prophylaxis.

OTHER SIDE-EFFECTS OF THALIDOMIDE

Peripheral neuropathy

This is a major potential problem with thalidomide as neuropathy can be irreversible if the drug is not promptly withdrawn. It is imperative that patients are monitored very closely, especially during the first few months of therapy. Patients must know that they should stop the drug if significant numbness or parasthesiae occur. However, the assessment of neuropathy in patients with myeloma is complex as neuropathy and other neurological symptoms are likely to be multifactorial in any given patient (e.g. vincristine effect, paraprotein-mediated neuropathy, amyloid, radicular or spinal cord compression, etc.). Certain guidelines, which have been published primarily with the use of thalidomide in chronic inflammatory disorders in mind (Powell & Gardner-Medwin, 1994), are probably inappropriate for patients with myeloma. For instance, it has been recommended that nerve conduction studies (NCS) should be repeated for each 10 g increment. This would translate to the requirement for NCS every 12–13 d in patients with myeloma, which is clearly both inappropriate and undesirable. The approach adopted by the UKMF is more pragmatic, and the MPT and T-VAD protocols state that the drug should be stopped if there are symptoms of peripheral neuropathy. In addition, it is recommended that NCS be performed at the earliest opportunity, ideally prior to commencing thalidomide, and should be repeated if necessary. However, for the patient who requires therapy, treatment should not be delayed if NCS cannot be performed immediately. Abnormal NCS in the absence of symptoms should not necessarily preclude the use of thalidomide if the potential benefits of therapy are considered significant, as if symptoms occur the drug can be stopped promptly. Prospectively performed NCS may help identify a particular pattern signifying those most at risk of developing neuropathy.

Sedation

As thalidomide was first introduced as a sedative agent, it is to be expected that somnolence is a common effect. The degree of sedation appears to decrease with continued administration at a constant dose and can be minimized by taking the drug in the evening. If the drug is taken approximately 3–4 h before going to bed, then any ‘hang-over’ effect is minimized for the following morning. This is frequently a dose-limiting side-effect.

Constipation

This can be a significant problem particularly when doses over 400 mg are taken. Again, the use of extra dietary fibre and laxatives can usually overcome this problem.

Birth defects

Dysmelia, particularly phocomelia, remains the most feared and devastating adverse event following thalidomide
exposure. Every effort must be made to ensure that patients are fully aware of this risk and that the drug is not given to women of child-bearing potential. If, after careful consideration of the potential risks and benefits, the drug is to be given to such women then extreme caution must be exercised with the use of two methods of contraception and regular pregnancy tests. With respect to myeloma, the overwhelming majority of affected women will be post-menopausal so that these particular risks will not be present. Nevertheless, patients must be clearly instructed to store the drug in a secure place and to return any unused drug to the hospital pharmacy. Men must be counselled to use barrier contraception if their partner is of child-bearing age as it is not known whether thalidomide is present in semen.

Neutropenia
This has been reported as a rare side-effect.

Hypothyroidism
One study has suggested that patients treated with thalidomide are at increased risk of developing biochemical and clinical hypothyroidism (Badros et al., 2000).

Rash
This has been most markedly noted when given in escalating doses with high-dose dexamethasone (Rajkumar et al., 2000b) but has been noted on occasions when used as a single agent.

Bradycardia
This has been reported as a side-effect.

CONCLUSIONS AND FUTURE PROSPECTS
Thalidomide has significant activity both as a single agent and in combination with other therapies in patients with de novo and advanced myeloma. However, several major questions remain unanswered. Indeed, the optimal dose is still uncertain, as is its role in maintenance therapy following high-dose melphalan. The potential benefit of combining thalidomide with dexamethasone as induction therapy for newly diagnosed patients with myeloma is being investigated by ECOG and results are awaited with considerable interest. Similarly, the combination of thalidomide with chemotherapy is still of uncertain benefit. All these questions need to be addressed in prospective randomized clinical trials before recommendations about the precise role of thalidomide can be given.

Thalidomide has a significant side-effect profile but is tolerated by the majority of patients. A minority of patients need to terminate treatment because of the development of peripheral neuropathy. So long as both physician and patient are aware of this potential problem, the drug can be stopped before severe, irreversible damage occurs. There seems little requirement for routine repeated nerve conduction studies in this setting. VTE has emerged as the most troublesome adverse event associated with the drug, particularly when thalidomide is used in combination with chemotherapy and/or dexamethasone as primary therapy for newly diagnosed patients. It is hoped that combined clinical and laboratory research will elucidate the mechanisms that result in a prothrombotic state and better delineate effective prophylactic measures.

Despite the difficulties and uncertainties, the use of thalidomide is a major advance in the clinical management of myeloma. Indeed, thalidomide represents a new paradigm for therapy in that it works primarily as a ‘biological’ agent rather than as a conventional cytotoxic drug. A series of alternative new ‘biological’ agents also show promise in myeloma and include proteosome inhibitors, bcl-2 antisense, angiogenesis inhibitors and farnesyl transferase inhibitors. In order to best define the utility of thalidomide and other new agents it is essential that they are tested appropriately in the context of prospective clinical trials.

SUMMARY AND RECOMMENDATIONS
• Thalidomide is an appropriate therapy for patients with relapsed or refractory disease.
• Patients not responding to thalidomide alone may respond to the combination of dexamethasone and thalidomide.
• It is not possible to make recommendations regarding the appropriate dose of thalidomide. However, the majority of patients will respond at doses of 300–400 mg or less and most patients are unable to tolerate doses greater than 600 mg.
• Thalidomide alone or in combination with dexamethasone should only be given to newly diagnosed patients in the context of a clinical trial.
• There is an increased risk of VTE in patients treated with thalidomide in combination with dexamethasone or other drugs, which varies in different patient groups and with different protocols.
• The mechanism of VTE is unexplained and at present it is not possible to make firm recommendations regarding antithrombotic prophylaxis.
• Routine serial nerve conduction studies are not practical for patients with myeloma, but clinical vigilance is essential to avoid serious neurotoxicity.

BRITISH COMMITTEE FOR STANDARDS IN HAEMATOLOGY (BCSH) HAEMATOLOGY/ONCOLOGY TASK FORCE
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References


Guideline


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