Review

Thalidomide in cancer medicine

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Thalidomide, an oral agent with antiangiogenic and immunomodulatory properties, is being investigated extensively in the management of advanced cancer. Multiple studies with large numbers of patients have confirmed that this drug has significant activity in multiple myeloma. Some patients with myelofibrosis or myeodysplastic syndromes may reduce their need for transfusions after thalidomide treatment. The activity of thalidomide in solid tumors is less prominent. Studies in Kaposi’s sarcoma, malignant melanoma, renal cell carcinoma and prostate cancer appear more promising especially when thalidomide is combined with biological agents or with chemotherapy. Limited activity was demonstrated in patients with glioma, while thalidomide appears to be inactive in patients with head and neck cancer, breast or ovarian cancer.

Key words: angiogenesis, antiangiogenic therapy, cancer, myeloma, thalidomide

Introduction

Thalidomide was introduced in Europe for the treatment of morning sickness in pregnant women but was withdrawn from the market in the 1960s because of reports of teratogenecity associated with its use. Many years later it was established that this complication was likely secondary to inhibition of blood vessel growth in the development of fetal limb buds [1]. Moreover, thalidomide was found to have immunomodulatory and anti-inflammatory properties [2]. These data prompted the evaluation of this agent in a variety of immune and neoplastic disease [3]. This review will focus on the role of thalidomide-based treatments in the management of human cancer.

Pharmacology

Thalidomide is a derivative of glutamic acid that exists as an equal mixture of enantiomers which rapidly interconvert at physiological pH [4]. Thalidomide is poorly soluble in water and thus no parenteral preparation is available. Maximum serum concentration of a 200 mg oral dose is reached within a mean of 4 h [5]. The drug undergoes rapid pH-dependent, spontaneous, non-enzymatic hydrolysis to multiple metabolites which are rapidly excreted in the urine, while non-absorbed drug is excreted in the feces. Clearance is primarily non-renal and the mean terminal half-lives of the two isomers are 4.6 and 4.8 h, respectively [3]. Studies in elderly prostate cancer patients showed that the volume of distribution and elimination half-life was significantly greater for the higher dose (1200 mg daily) than for the lower dose (200 mg daily) [5, 6].

Mechanism of action

The mechanism of action of thalidomide is complex and it probably includes different molecular targets [3]. D’Amato et al. first reported that thalidomide inhibits angiogenesis by interrupting processes mediated by bFGF and/or vascular endothelial growth factor (VEGF) [1]. Moreover, thalidomide inhibits TNF-α synthesis by inducing TNF-α mRNA degradation [7]. Recent data suggest that this drug can block the activation of nuclear factor (NF)-κB through a mechanism involving the inhibition of IκB kinase activity [8]. Thalidomide downregulates surface adhesion molecules in experimental models [9]. It co-stimulates human T cells, including cell proliferation mainly of the CD8+ subset, and stimulates IL-2 and IFN-γ production. Reduction of other cytokines, such as IL-6 and IL-12, are inhibited by thalidomide. Moreover, this agent reduces free radicals that may cause oxidative DNA damage [3].

Side-effects

Thalidomide causes a variety of side-effects which are summarized in Table 1. Thalidomide is a known teratogenic agent and its use is absolutely contraindicated in pregnant women. All patients must be registered on the System for Thalidomide Education and Prescribing Safety (STEPS) program before thalidomide may be prescribed [10]. Women of childbearing potential (<2 years postmenopausal) must have a negative
Table 1. Side-effects of thalidomide

<table>
<thead>
<tr>
<th>System</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral nervous</td>
<td>Numbness, paresthesia, pain in the extremities, burning sensation (30%)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Hangover feeling, nervousness, tremor (10%), confusion, aural buzzing, fatigue (20–50%), depression (5–20%), dizziness, somnolence (&gt;50%), headache, sedation, fluctuation of blood pressure (5%), bradycardia (5%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Constipation (&gt;50%), nausea (5–20%), increased appetite, xerostomia (10%)</td>
</tr>
<tr>
<td>Hematological</td>
<td>Deep vein thrombosis (5–30%), neutropenia (&lt;5%), granulocytopenia (&lt;5%)</td>
</tr>
<tr>
<td>Skin</td>
<td>Red palms, skin rash (25%), toxic epidermal necrolysis (1%), brittle fingernails, pruritus (20–50%)</td>
</tr>
<tr>
<td>Genital system</td>
<td>Teratogenicity, phocomelia, menstrual irregularities, decreased libido</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypothyroidism (5–20%), edema (5–20%)</td>
</tr>
</tbody>
</table>

*Percentages in parentheses show the frequency of each side-effect as reported in the literature.

pregnancy test prior to starting thalidomide, and they must be using two effective forms of birth control and followed every 4 weeks with a pregnancy test. Men receiving thalidomide must practice abstinence or use of a latex condom.

As thalidomide was first introduced as a sedative agent, this is a frequently reported side-effect. The severity of sedation appears to decrease with continued administration at a constant dose and can be minimized by taking the drug in the evening approximately 3–4 h before going to bed, although somnolence and fatigue may be a problem the following day. Constipation is a common side-effect and its severity may be dose-related. Patients should be advised to have high fiber diet and to use laxatives prophylactically.

Dry skin and pruritus are frequently noted and can be minimized by using non-alcohol-based lubricants. Relatively frequent skin eruptions include morbilliform, seborrheic, maculopapular or nonspecific dermatitis. Severe skin reactions, i.e. erythema multiforme and toxic epidermal necrolysis are rare.

The most serious adverse effects associated with thalidomide are deep vein thrombosis (DVT) and peripheral neuropathy. DVT has been reported in ~5% of patients with previously treated myeloma who receive single-agent thalidomide. A recent report on a large number of patients with myeloma treated with thalidomide and cytotoxic chemotherapy documented DVT in 15% of patients. A multivariate analysis of potential predisposing factors indicated that the combination of thalidomide with doxorubicin-containing chemotherapy was the most significant variable. Furthermore, newly diagnosed disease and chromosome 11 abnormality were also independent factors whereas there was no relationship with central venous lines. The development of DVT did not adversely affect survival [11]. It appears that aspirin or low dose warfarin are ineffective, whereas therapeutic anticoagulation with warfarin, or with low molecular weight heparin, can prevent DVT in almost all patients.

Peripheral neuropathy is more frequent in patients with neuropathy from other causes; it is dose-dependent and affects 10–50% of patients. The most frequent symptoms are numbness and paresthesia which can be reversible after prompt withdrawal of the drug. Thus patients should be advised to stop the drug if there are symptoms of progressively worsening peripheral neuropathy. Tingling may also be noted earlier in the course of treatment. This symptom may be due to poor circulation and it often improves with ambulation [12]. Electrophysiological studies have shown that thalidomide causes a length-dependent predominantly sensory axonal neuropathy that affects large and small fibers [13]. In a prospective study of prostate cancer patients treated with thalidomide, it was found that a decline of sensory nerve action potentials (SNAP) and clinical symptoms occurred concurrently. Thus, it appeared that the SNAP index can be used to monitor peripheral neuropathy, but not for early detection [14]. We believe that further prospective studies are required in order to establish the role of nerve conduction studies in the identification of patients at higher risk for peripheral neuropathy, early detection and monitoring of this complication.

Thalidomide use in hematological malignancies

Multiple myeloma

Singhal et al. first reported that thalidomide induced partial or complete responses in ~30% of patients with refractory myeloma. Most of these patients had failed high-dose therapy [15]. Several other studies have confirmed these results (Table 2) [16–18]. The median time to response after treatment with thalidomide is 2–4 months. Thalidomide was originally administered daily at bedtime at a starting dose of 200 mg with 200 mg increments every 2 weeks to a maximum dose of 800 mg [15]. Since several side-effects are age- and dose-related, nearly half of the patients are unable to receive the maximum 800 mg dose [12]. Some studies have indicated that there is a dose–response effect [16]. Other studies reported similar activity with lower doses [12]. Thus the optimal dose of thalidomide has not been established. Outside the context of a clinical study, thalidomide therapy should be individualized to a dose that achieves response and is well tolerated. At the MD Anderson Cancer Center, the response rate with doses ≤400 mg/day was similar to that with higher doses. However, toxicity nearly doubled at daily doses >400 mg [18]. We recommend a starting dose of thalidomide of 200 mg with 100 mg increments every week to a maximum dose of 400 mg daily. The daily dose should be adapted to tolerability which in most patients is between 200 and 400 mg/day. Median survival of thalidomide-treated patients exceeds 1 year.
Myeloma

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of patients</th>
<th>Regimen</th>
<th>Thal max dose, mg/day</th>
<th>OR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singhal et al. [15]</td>
<td>84</td>
<td>Thal</td>
<td>800</td>
<td>25</td>
</tr>
<tr>
<td>Barlogie et al. [16]</td>
<td>169</td>
<td>Thal</td>
<td>800</td>
<td>30</td>
</tr>
<tr>
<td>Schey et al. [17]</td>
<td>69</td>
<td>Thal</td>
<td>600</td>
<td>28</td>
</tr>
<tr>
<td>Dimopoulos et al. [19]</td>
<td>44</td>
<td>Thal+Dexa</td>
<td>400</td>
<td>55</td>
</tr>
<tr>
<td>Palumbo et al. [20]</td>
<td>120</td>
<td>Thal+Dexa</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>Moehler et al. [21]</td>
<td>56</td>
<td>Thal+Chemo</td>
<td>400</td>
<td>64</td>
</tr>
<tr>
<td>Kropff et al. [22]</td>
<td>60</td>
<td>Thal+Chemo</td>
<td>400</td>
<td>64</td>
</tr>
<tr>
<td>Untreated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rajkumar et al. [24]</td>
<td>31</td>
<td>Thal</td>
<td>800</td>
<td>33</td>
</tr>
<tr>
<td>Weber et al. [25]</td>
<td>28</td>
<td>Thal</td>
<td>600</td>
<td>36</td>
</tr>
<tr>
<td>Weber et al. [25]</td>
<td>40</td>
<td>Thal+Dexa</td>
<td>400</td>
<td>72</td>
</tr>
<tr>
<td>Rajkumar et al. [26]</td>
<td>50</td>
<td>Thal+Dexa</td>
<td>200</td>
<td>64</td>
</tr>
<tr>
<td>Zervas et al. [27]</td>
<td>39</td>
<td>Thal+VAD</td>
<td>200</td>
<td>74</td>
</tr>
<tr>
<td>MMY</td>
<td>HI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barosi et al. [36]</td>
<td>21</td>
<td>Thal</td>
<td>400</td>
<td>43</td>
</tr>
<tr>
<td>Canepa et al. [37]</td>
<td>10</td>
<td>Thal</td>
<td>800</td>
<td>30</td>
</tr>
<tr>
<td>Piccaluga et al. [39]</td>
<td>12</td>
<td>Thal</td>
<td>600</td>
<td>60</td>
</tr>
<tr>
<td>Elliott et al. [38]</td>
<td>15</td>
<td>Thal</td>
<td>400</td>
<td>80</td>
</tr>
</tbody>
</table>

Chemo, chemotherapy; dexa, dexamethasone; HI, hematological improvement; max, maximum dose; MMY, myelofibrosis with myeloid metaplasia; OR, objective response; thal, thalidomide; VAD, vincristine, dexamethasone, and liposomal doxorubicin.

Prognostic factors associated with longer survival include low serum β2 microglobulin levels, absence of cytogenetic abnormalities involving chromosome 13, younger age and low plasma cell labeling index [16].

The activity of thalidomide as single agent in advanced myeloma, along with in vitro evidence of synergism with dexamethasone, provided the rationale for investigation of the combination of thalidomide with dexamethasone (TD). Several reports have indicated that this combination was active in ~50% of patients with refractory or relapsing myeloma. Moreover, the addition of dexamethasone to thalidomide reduced the median time to response to 1 month, or even less, and reduced the daily dose of thalidomide and therefore the incidence of thalidomide-related side-effects [19, 20]. Nevertheless, it is not clear whether TD improves event-free or overall survival compared with treatment with thalidomide alone. Thalidomide and dexamethasone have also been combined with chemotherapy for the treatment of patients with refractory myeloma. Several series have added cytotoxic drugs such as cyclophosphamide, etoposide, doxorubicin and cisplatin. Objective responses have been documented in at least two-thirds of patients and median survival exceeds 18 months [21–23]. However, it is not clear whether the addition of chemotherapy to thalidomide actually improves survival, while these combinations are complicated with myelosuppression and infections in addition to the thalidomide-related side-effects. Furthermore, the risk of DVT is increased compared to thalidomide alone.

In view of the significant activity of thalidomide in refractory and relapsing myeloma, this agent has been administered to previously untreated patients alone or in combination with other agents. Two phase II studies have used single-agent thalidomide in patients with smouldering or asymptomatic myeloma and showed partial responses in one-third of patients [24, 25]. The Mayo Clinic series showed a 2-year progression-free survival of 63% for patients treated with thalidomide as opposed to 47% for untreated historical controls [24]. However, patients with smouldering or asymptomatic myeloma should not be treated with thalidomide outside the context of a clinical trial.

The TD regimen has been administered to previously untreated patients; 60–70% of patients have achieved objective responses, the median time to response was <1 month and adequate numbers of blood stem cells were collected from patients eligible for subsequent high-dose chemotherapy [25, 26]. This oral, non-myelosuppressive regimen may be used as primary treatment for multiple myeloma when blood stem cell collection is planned, if there is evidence of neutropenia or thrombocytopenia or when concomitant radiotherapy is required. No more than 4 months of treatment with high dose dexamethasone and no more than 400 mg of daily thalidomide are recommended. There are preliminary reports on the addition of cytotoxic drugs to TD in previously untreated patients with multiple myeloma. Zervas et al. have added thalidomide at a daily dose of 200 mg to vincristine and dexamethasone (VAD) with liposomal doxorubicin and observed a 74% objective response rate including complete responses in 10% of patients [27]. Palumbo et al. have added thalidomide at a daily dose of 100 mg to melphalan and prednisone and reported a 90% objective response rate (22% complete responses). The incidence of DVT was 20% [28]. The largest randomized study is being conducted at the University of Arkansas. Patients are treated with sequential chemotherapy and tandem autotransplants with or without thalidomide, which is being administered at a daily dose of 100 mg. So far, response and survival data are not available, but a high rate of DVT has been reported among patients receiving thalidomide (28% versus 4%) [29]. Lastly, TD has been administered to patients whose disease was in persistent partial response after myeloablative therapy with blood stem cell support. Fifty-seven percent of patients had marked further reduction of myeloma protein by >90%, including four patients who achieved complete response [30]. A UK Myeloma Forum phase II study evaluated five dose levels of single-agent thalidomide after high-dose therapy and indicated that a daily dose of 200 mg can be used for maintenance with a relatively low toxicity-related drop out rate [31]. A randomized trial is planned to answer the role of thalidomide on disease-free and overall survival.
Waldenstrom’s macroglobulinemia

Waldenstrom’s macroglobulinemia (WM) is a lymphoplasmacytic lymphoma that shares similarities with multiple myeloma. Dimopoulos et al. performed a phase II clinical trial with 20 WM patients. The drug was started at a dose of 200 mg/day with dose escalation as tolerated to a final dose of 600 mg/day [32]. Five patients experienced a partial response after treatment. Side-effects were significant, mainly in the elderly, and only low doses of thalidomide were tolerated. All responding patients experienced improvement within 2 months. The median duration of response was 11 months. In a subsequent study, 12 pretreated patients with WM received clarithromycin (500 mg twice a day), low dose thalidomide (200 mg/day) and dexamethasone (40 mg/week). Three patients (25%) experienced a partial response (≥50% reduction of tumor infiltrate) and two other patients had a minor response [33].

AL amyloidosis

Thalidomide has also been administered to a limited number of patients with AL amyloidosis. In one study a significant reduction of Bence Jones proteinuria was observed in 25% of patients. However, none of these patients had a significant reduction in their nephrotic range proteinuria [34]. In addition, 50% of patients experienced grade 3 or 4 toxicity and 25% discontinued thalidomide due to side-effects. Fatigue and other central nervous toxicities represented the major dose-limiting toxicities.

In another study dexamethasone pulses were added to thalidomide which was started at 100 mg daily with 100 mg increments every 2 weeks up to 400 mg. Monoclonal protein response was noted in 59% of patients along with >50% reduction of proteinuria in all affected patients. Severe side-effects including bradycardia necessitated interruption of treatment in 65% of patients. Six patients who received 400 mg responded, while there were no responders among the four patients who received 100 mg daily [35]. Thus standard dose thalidomide is poorly tolerated by patients with amyloidosis. Whether low dose single-agent thalidomide with, or without, dexamethasone may be tolerated better and may result in organ responses require further study.

Myelofibrosis with myeloid metaplasia

Myelofibrosis with myeloid metaplasia (MMM) is a myeloproliferative disorder associated with bone marrow fibrosis, ectopic hematopoiesis and increased microvascular density. Several phase II studies have assessed the efficacy and tolerability of thalidomide in MMM (Table 2) [36–39]. Improvement of thrombocytopenia and of anemia appeared to be the main benefit from this treatment. Regression significant splenomegaly was noted in <20% of patients. Untoward hematological effects such marked leukocytosis and thrombosis have occurred in some patients. Furthermore, up to 50% of patients have discontinued thalidomide because of side-effects. Thus, several studies have confirmed that thalidomide is associated with clinical benefit in patients with MMM but its tolerability is a major issue in this disease. Furthermore, thalidomide appears to be ineffective in myelofibrosis arising in the course of polycythemia vera or in patients with MMM causing massive splenomegaly [36–39].

A phase II trial by Mesa et al. investigated the impact and tolerability of low dose thalidomide and prednison in patients with MMM [40]; 21 patients received thalidomide at a dose of 50 mg/day as well as 3-month oral prednison. Thalidomide and prednison were well tolerated and 13 patients (62%) responded. Among 10 transfusion-dependent patients seven improved and four became transfusion-independent; six of eight patients with thrombocytopenia achieved a ≥50% increase in their platelet count; four of 21 patients achieved a spleen reduction by >50%. Low doses of thalidomide and prednisonseem to be better tolerated, improving in parallel the therapeutic outcome. Thalidomide and prednisone require further evaluation in earlier stages of MMM. This combination is a reasonable therapeutic choice for patients with MMM whose main manifestation is cytopenia.

A long-term outcome analysis of two Mayo Clinic trials which included 36 patients indicated that thalidomide with or without concomitant prednison resulted in an overall response in 19 patients (53%). Moreover, 19% of patients remained in unmaintained remission without additional medication at a median of 17 months after stopping thalidomide [41].

Myelodysplastic syndrome

The immunomodulatory and antiangiogenic potency of thalidomide prompted its evaluation in the management of myelodysplastic syndromes (MDS). In a large study, Raza et al. treated 83 MDS patients with thalidomide. Thalidomide was given at a starting dose of 100 mg/day and increased up to a maximum of 400 mg/day, if tolerated [42]. Fifty-one patients completed 3 months of therapy. The overall response rate was 19%; 15 patients achieved erythroid response, 10 became transfusion independent and one had an increase in platelet count. The responses lasted for a median of 306 days. Patients who were more likely to benefit were those with lower blasts and higher baseline platelet counts. Zorat et al. administered thalidomide to 30 patients with MDS. Ten patients experienced erythroid response and six became transfusion independent. Clinical response was more often in patients with a higher baseline platelet count and a lower percentage of blasts [43]. Stupp et al. treated 34 patients and observed hematological improvement in 56%. Responders experienced an amelioration of quality of life [44]. Combination of darbopoietin with thalidomide in patients with MDS was associated with increased incidence of DVT in a recent study [45]. Based on the available data, it would be reasonable to administer thalidomide in patients with refractory cytopenias. However, more studies are needed on the effect of thalidomide on cytogenetic response and progression of MDS to acute leukemia.

The therapeutic efficacy of thalidomide monotherapy in MDS patients encouraged its evaluation combined with chemotherapy in poor prognosis acute myeloid leukemia or MDS patients. Thalidomide was initiated at a dose of 400 mg/day
and escalated up to 600 mg/day, if tolerated; 17 of 37 patients treated with daunorubicin and ara-c and 16 of 36 patients treated with daunorubicin, ara-c and thalidomide experienced complete remission. Median response duration and survival were similar in both arms. These results indicate no benefit from the addition of thalidomide to chemotherapy in poor prognosis MDS patients [46].

**Acute myeloid leukemia**

Recent data suggest an involvement of angiogenesis in the pathophysiology of acute myeloid leukemia (AML). Twenty patients with poor risk AML received thalidomide at a daily dose of 200–400 mg. Four patients achieved a partial response, defined as reduction of leukemic bone marrow infiltration accompanied by improvement of red blood cell and platelet counts [47]. A recently reported trial of thalidomide in 16 patients with refractory or relapsed AML showed one complete response lasting 36 months and a transient reduction in marrow blasts in two additional patients. There was no correlation between reduction in levels of angiogenesis and response [48]. Thus, administration of thalidomide in AML is not recommended outside the context of clinical trials.

**Thalidomide in solid tumors**

It is now well established that angiogenesis plays a major role in the aggressive behavior and metastatic potential of various solid tumors. These findings provide the rationale for evaluating thalidomide in the treatment of solid tumors. Nevertheless, the data are more limited compared to those on hematological malignancies (Table 3).

**Brain tumors**

It has been shown that glioma and glioblastoma are highly vascularized tumors that overexpress angiogenic factors. These data provide the rationale for the evaluation of antiangiogenic factors, such as thalidomide, in the treatment of glioma and glioblastoma. Monotherapy with thalidomide has been studied in three phase II trials including patients with recurrent glioma, astrocytoma or glioblastoma multiforme [49–51]. Most patients had evidence of radiological progression and had previously received some form of treatment (surgery, radiotherapy, chemotherapy). The daily dose was from 100 to 1200 mg. Thalidomide was generally well tolerated but objective responses were rare. In one of these studies, eight of 39 patients (20%) were alive >1 year after initiation of thalidomide and median survival was 7 months.

**Table 3. Activity of thalidomide in solid tumors, alone or in combination**

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of patients</th>
<th>Regimen</th>
<th>Thal max dose, mg/day</th>
<th>OR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine et al. [49]</td>
<td>36</td>
<td>Thal</td>
<td>800–1200</td>
<td>12 (33 SD)</td>
</tr>
<tr>
<td>Short et al. [50]</td>
<td>18</td>
<td>Thal</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>Marx et al. [51]</td>
<td>42</td>
<td>Thal</td>
<td>100–500</td>
<td>5 (42 SD)</td>
</tr>
<tr>
<td>Fine et al. [53]</td>
<td>40</td>
<td>Thal+BCNU</td>
<td>800–1200</td>
<td>24</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stebbing et al. [54]</td>
<td>25</td>
<td>Thal</td>
<td>600</td>
<td>9</td>
</tr>
<tr>
<td>Motzer et al. [55]</td>
<td>26</td>
<td>Thal</td>
<td>800</td>
<td>62 (SD only)</td>
</tr>
<tr>
<td>Daliani et al. [57]</td>
<td>20</td>
<td>Thal</td>
<td>1200</td>
<td>10</td>
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<tr>
<td>Escudier et al. [56]</td>
<td>40</td>
<td>Thal</td>
<td>1200</td>
<td>5</td>
</tr>
<tr>
<td>Minor et al. [58]</td>
<td>29</td>
<td>Thal</td>
<td>1200</td>
<td>5</td>
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<tr>
<td>Prostate cancer</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Figg et al. [65]</td>
<td>63</td>
<td>Thal</td>
<td>1200</td>
<td>27</td>
</tr>
<tr>
<td>Drake et al. [64]</td>
<td>20</td>
<td>Thal</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>Figg et al. [66]</td>
<td>36</td>
<td>Thal+Docetaxel</td>
<td>200</td>
<td>53</td>
</tr>
<tr>
<td>Melanoma</td>
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</tr>
<tr>
<td>Hwu et al. [68]</td>
<td>38</td>
<td>Thal+Temozolomide</td>
<td>250</td>
<td>10</td>
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<tr>
<td>Danson et al. [69]</td>
<td>60 (Thal arm)</td>
<td>TMZ versus Thal/TMZ versus IFN/TMZ</td>
<td>100</td>
<td>25</td>
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<td>Kaposis’s sarcoma</td>
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<td>Fife et al. [70]</td>
<td>17</td>
<td>Thal</td>
<td>100</td>
<td>35</td>
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<tr>
<td>Little et al. [71]</td>
<td>20</td>
<td>Thal</td>
<td>1000</td>
<td>47</td>
</tr>
</tbody>
</table>

BCNU, bis-chloro-ethyl nitrosourea; Max, maximum dose; IFN, interferon α-2b; OR, objective response; SD, standard deviation; thal, thalidomide; TMZ, temozolomide.
Glass et al. combined thalidomide up to a dose of 300 mg/day with carboplatin for recurrent glioma. A partial response was documented in 11% of patients and the median overall survival was 40 weeks [52]. Fine et al. studied the therapeutic impact of thalidomide combination with carmustine (BCNU) on 40 patients with progressive high-grade gliomas after previous radiotherapy or surgery [53]. Patients received carmustine 200 mg/m² on day 1 of every 6-week cycle, and thalidomide 800 mg/day, that was increased up to 1200 mg/day, if tolerated; 24% of patients achieved response to therapy (including one complete response and seven partial responses) and the median progression-free survival was 100 days. The therapeutic combination was well tolerated despite the fact that thromboembolic events occurred in 12 patients (30%).

These data show that single-agent thalidomide has minimal activity in high-grade gliomas and that combinations of thalidomide with chemotherapy deserve further study.

Renal cell carcinoma

The highly vascular nature of renal cell carcinoma (RCC) and its resistance to chemotherapy during the metastatic stage makes it a possible candidate for thalidomide treatment. Seven phase II studies have evaluated this agent in patients with metastatic RCC (Table 3). The target daily dose ranged from 600 to 1200 mg; toxicity was significant with peripheral neuropathy representing the most serious long-term side-effect. Partial response rate ranged from 0% to 17% among different studies. Furthermore 17–64% of patients have been rated as stable disease [54–59]. However, it should be noted that disease stabilization occurs as part of the natural history of metastatic RCC.

Combination trials of thalidomide with other agents, such as IFN-α or IL-2, have been recently completed or are ongoing. The combination of IFN-α at a dose of 9 MIU, given three times a week with continuous thalidomide to a maximum dose of 400 mg/day, resulted in serious and unexpected adverse events including seizures and visual disturbances [60]. In another study IFN-α and thalidomide were both administered at low doses to 30 patients with metastatic RCC. A partial response was noted in 22% of assessable patients and 63% of patients had stable disease for ≥3 months. The median time to treatment failure was 7.7 months and the most common side-effect was neurotoxicity. Serum VEGF levels decreased more in patients who responded to therapy compared with those patients whose condition remained stable or progressed early [61]. A randomized trial conducted by the Eastern Cooperative Oncology Group comparing IFN plus thalidomide versus IFN alone has completed accrual and results are awaited. Amato et al. combined thalidomide at a daily dose of 400 mg with IL-2 given subcutaneously at low doses, and reported a 42% objective response rate [62]. An ongoing randomized trial is comparing thalidomide with low-dose IL-2 versus low-dose IL-2 alone versus thalidomide alone in previously untreated metastatic RCC.

In conclusion, single-agent thalidomide has modest activity in RCC and the administration of thalidomide in patients with metastatic RCC refractory to other regimens is reasonable. Activity of thalidomide in combination with IFN-α and especially with IL-2 is promising but results of ongoing randomized trials are needed.

Prostate cancer

Several studies have indicated that tumor angiogenesis correlates with metastasis in prostate cancer [63]. Thalidomide has been administered to patients with hormone-refractory prostate cancer. A phase II study showed that low-dose thalidomide may be an option for such patients since 37.5% of patients showed a fall in prostate-specific antigen (PSA) including 15% of patients with a PSA decline of at least 50% [64]. A phase II randomized trial comparing low-dose (200 mg/day) and high-dose (up to 1200 mg/day) thalidomide in hormone-refractory prostate cancer showed a PSA reduction of >50% in 18% of patients treated with low-dose thalidomide. The high-dose arm demonstrated no PSA reduction although side-effects limited dose escalation above 200 mg/day in 30% of patients in this group [65].

Because angiogenic activity is thought to be greatest when tumor load is low it was hypothesized that the combination of an active cytotoxic agent with an anti-angiogenic agent may be more effective than either treatment alone. An ongoing phase II randomized study is evaluating weekly docetaxel with or without thalidomide at a dose of 200 mg/day. Serum PSA reduction was seen in 35% and 53% of patients receiving single-agent and combination treatment, respectively. The observation that thromboembolic events occurred in 20% of patients receiving thalidomide and docetaxel prompted the administration of prophylactic anticoagulation [66].

An ongoing randomized study is assessing the ability of thalidomide to prolong the time to PSA rise in patients with prostate cancer and rising PSA following primary treatment but without over metastatic disease. Patients will receive intermittent hormonal therapy and will be randomized to placebo or thalidomide when off of hormonal therapy [63]. This study will show whether thalidomide may have a cytostatic role in low-volume prostate cancer.

We conclude that early clinical trials show that low dose thalidomide appears to be relatively well tolerated and it shows activity in hormone refractory prostate cancer which may be similar to single-agent chemotherapy. The observation of increased response rate when thalidomide was added to docetaxel supports the role on how thalidomide can influence the activity of chemotherapy.

Melanoma

Thalidomide has negligible single-agent efficacy in advanced melanoma [57]. Nevertheless, when this agent is combined with temozolomide efficacy can be improved. Encouraging results have been reported in a dose-finding study [67]. Five major responses were documented among the 12 patients included. This study was followed by a phase II study combining daily temozolomide at 75 mg/m² with thalidomide.
100–400 mg [68]. The second study confirmed the activity of the combination with a 32% response rate. Furthermore, the activity and tolerability of the thalidomide–temozolomide combination was shown in a recent randomized phase II study. Danson et al. compared the combination of temozolomide with either IFN-α-2b or thalidomide in 181 patients with metastatic melanoma: 60 patients received thalidomide 100 mg/day and temozolomide at a dose of 150 mg/m² (increased to 200 mg/m² after the first cycle). Median survival was 7.3 months for the combination temozolomide–thalidomide and 1-year survival was 24%; 16% of patients were alive for 2 years after randomization. Response or disease stabilization occurred in 25% of patients receiving thalidomide–temozolomide. This combination was considered the most suitable for future studies [69].

The results of the above studies suggest that thalidomide combined with temozolomide has some efficacy in melanoma and further studies could determine its role in the management of this disease.

Kaposi’s sarcoma

During clinical trials with thalidomide administered to HIV patients, activity against Kaposi’s sarcoma was noted. Fife et al. performed a phase II trial with 17 patients with cutaneous AIDS-related Kaposi’s sarcoma [70]. Thalidomide was administered at a dose of 100 mg/day for 8 weeks and six patients experienced a partial response. In another phase II dose escalation study 20 HIV seropositive patients received an initial dose of thalidomide 200 mg/day, which was increased to a final dose of 1000 mg/day for up to a year. Eight of 17 assessable patients achieved a partial response, and the other two patients had stable disease. The median duration of drug treatment was 6.3 months and the median time to progression was 7.3 months. Drowsiness and depression were the most frequent side-effects [71]. Thalidomide seems to be effective in Kaposi’s sarcoma and further studies could determine the appropriate dose for achieving the maximum therapeutic benefit without excessive adverse effects.

Other solid tumors

Few reports on the activity of thalidomide in patients with other solid tumors have been published so far. These studies showed no single-agent activity in metastatic breast and head and neck carcinomas [59, 72, 73]. Single-agent thalidomide was inactive in heavily pretreated metastatic colorectal cancer [74]. Another study, which has been reported in abstract form, suggested promising efficacy of the combination of thalidomide and irinotecan in patients with advanced colorectal cancer previously treated with fluorouracil. Furthermore, thalidomide ameliorated irinotecan-related toxicity [75]. Single-agent thalidomide treatment in unresectable and non-embolizable hepatocellular carcinoma was associated with an objective response rate of 6.3% and 12% of patients had a >50% decrease in their α-fetoprotein levels. All responses occurred at a dose ≤300 mg/day. Low-dose thalidomide induced an unequivocal tumor response in a minority of patients with advanced HCC [76].

Supportive care in graft-versus-host disease (GVHD) and palliative care in cancer cachexia

Thalidomide immunomodulatory properties provided the rationale for its evaluation in GVHD. Rovelli et al. administered thalidomide to 14 children with refractory and/or high risk chronic GVHD (cGVHD) [77]. Six children achieved complete response and an additional four had partial response. Thalidomide was increased up to a maximum of 800 mg/day. The best responders had mainly mucotaneous involvement and less severe cGVHD.

In a recent clinical trial, Kulkarni et al. investigated the efficacy of thalidomide on cGVHD and acute GVHD (aGVHD) [78]. Thalidomide was prescribed at a starting dose of 150–300 mg/day, which was gradually escalated up to 1200 mg/day, if tolerated. There were no clinical responses among patients with acute GVHD. Thirteen patients with cGVHD (22%) experienced complete response and eight had partial response. Clinical studies confirmed thalidomide efficacy in cGVHD and its lack of efficacy in aGVHD.

Thalidomide efficacy in inhibiting and reversing weight loss in AIDS-associated cachexia induced its evaluation as a palliative therapy in end stage cancer patients. Cancer cachexia presents with symptoms such as anorexia, asthenia, chronic nausea and hyper catabolic state resulting in weight loss and deterioration of quality of life. Bruera et al. performed a study including 72 patients to evaluate thalidomide impact on cancer cachexia. Patients received low dose thalidomide of 100 mg/day. Thalidomide was generally well tolerated and reduced insomnia (69%) and nausea (44%) and improved appetite (63%) and sensation of well being (53%) [79]. The effect of thalidomide may be due to the reduction of cytokines, which may be important mediators of cancer cachexia.

Conclusions: future prospects

Although thalidomide has shown antitumor activity in several hematological malignancies, a clear benefit for patients has only been demonstrated in multiple myeloma. Furthermore, promising activity has been shown in MMM and MDS. Low dose thalidomide combined with prednisone may become a useful treatment for MMM. Preliminary reports in patients with refractory multiple myeloma indicate that thalidomide can be combined with the proteasome inhibitor bortezomib or with the antisense oligonucleotide oblimersen sodium which targets Bcl-2. Such combinations are associated with significant activity even in thalidomide-resistant patients [80, 81]. Several phase II studies in solid tumors have indicated activity in Kaposi’s sarcoma, RCC and prostate cancer. Ongoing trials which are evaluating combinations of thalidomide with other active cytotoxic agents, IFN or IL-2 will define the role of
thalidomide in prostate cancer, melanoma and renal cell carcinoma.

Despite the multiple possible mechanisms of action, knowledge with regard to the molecular targets of thalidomide remains incomplete. There is strong evidence that thalidomide requires cytochrome P450(CYP)-catalyzed biotransformation to exert its pharmacological activity and that the CYP2C sub-family may be primarily involved. Furthermore, there is evidence of pharmacogenetic association of CYP2C19 genotype with the in vivo metabolism and activity of thalidomide in patients with prostate cancer [82]. Further studies may help exclude patients with the poor metabolizer genotype who are unlikely to respond to thalidomide. Moreover, research focuses on the development of new analogs of thalidomide with improved efficacy and reduced toxicity. Some of the immunomodulatory drugs are 1000-fold more potent than thalidomide in blocking TNF-α immunomodulatory drugs are 1000-fold more potent than thalidomide [4]. One such analog, CC-5013, has already shown promise in myeloma and myeloid dysplastic syndromes.

References


