Thalidomide: from tragedy to promise

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Summary

Thalidomide is an immunomodulatory and antiangiogenic drug. Although the exact mechanism of action is not fully understood, it has been shown to be active in a variety of diseases. There are multiple trials going on to evaluate the optimal dose of thalidomide and the importance of combining thalidomide with other drugs. This review introduces the properties and putative mechanism of action of thalidomide and summarizes the most important clinical trials with this biological modifier.

Key words: thalidomide; Contergan®; immunomodulation

Historical background

Thalidomide (Contergan®) was first introduced in 1956 by Chemie Gruenenthal GmbH as a potent and apparently safe non-barbiturate sedative-hypnotic in West Germany. Animal experiments had shown that the main difference between thalidomide and other hypnotics was its extremely low acute toxicity. It gained widespread popularity in Europe and Canada. In 1960 the sales in Germany amounted to 14.6 tons. Thalidomide could be purchased without a prescription. Later on, it became also popular in the treatment of pregnancy-related morning sickness.

In the United States, the FDA (Food and Drug Administration) did not approve thalidomide for clinical use because of reports of tingling hands and feet in people who used this drug over long periods of time.

In 1961 Mc Bride and Lenz, two physicians working independently of each other, realized a link between the consumption of this drug and the birth of children with missing digits, arms and legs and deformities of internal organs (phocomelia). Worldwide 8000–10000 children in total were born with malformations of the bodyrelated to the use of thalidomide. When the severe teratogenic potential was realized, thalidomide was immediately withdrawn from the markets in Europe and Canada [1–4].

In 1965 the unexpected activity of thalidomide in reactive lepromatous leprosy stimulated further studies. After some confirmatory placebo-controlled trials thalidomide was finally approved in 1997 by the FDA as treatment of erythema nodosum leprosum [5]. This stimulated new interest in thalidomide for the treatment of other inflammatory and autoimmune diseases. In addition thalidomide was used in many other diseases with a main interest in cancer. To guarantee the safe application and use of thalidomide, a special educational booklet was created by Celgene Cooperation, the main producer of thalidomide in the US. Because of the potential teratogenicity, patients must adhere to this booklet (System for thalidomide Education and Prescribing Safety [STEPS]) [6]. However in other countries like Brazil the poorly supervised use of thalidomide for leprosy in uneducated patients is causing an unknown number of children with the typical severe birth defects even nowadays [7].

Pharmacokinetics

Thalidomide [2-(2,6-dioxo-piperidine-3-yl)-iso-indole-1,3-dione] has the empirical formula C13H10N2O4 (fig. 1). It is a racemic mixture with presumed differential activities of the (−)-(S)- and (+)-(R)-isomers. Because of its lipophilic structure the water solubility of thalidomide is very poor.

The bioavailability seems to be dependent on the dose, the food that is ingested together with the drug (high fat meals lead to an increase of T_{max} of 6 hours), and concurrent illnesses of the patient (e.g. maldigestion).

Low doses (100 mg) are slowly absorbed in the gastrointestinal tract. The time to peak plasma
concentration ($T_{max}$) is between 2 and 4 h; the maximal plasma concentration ($C_{max}$) is about 1 µg/ml.

The mean bioavailability by rectal application compared to oral application is below 40% [9].

Thalidomide is very susceptible to hydrolysis. In theory about 100 possible metabolites of thalidomide may be found in the plasma by spontaneous non-enzymatic hydrolysis.

The metabolites are species-specific. This fact explains the species-specific actions of thalidomide [10, 11].

Pharmacodynamics

The mechanism of action of thalidomide is not entirely understood and seems to be related to immune modulation, changes in cytokine levels and antiangiogenesis [15].

The immunomodulatory effects of thalidomide are controversially discussed and depend greatly upon the conditions used for examination.

Immunomodulatory effects on lymphocytes include a decrease in circulating CD4 positive T-cells [16] and a stimulation of CD8 positive T-cells [17], thus leading to a decreased CD4/CD8 ratio. In addition thalidomide seems to induce a shift from T helper cell type 1 (Th1) to Th2 T-cell responses, i.e. a change from a more cytotoxic T-cell dominated immune response triggered mainly by Interferon-$\gamma$ to a mainly antibody mediated immune response, triggered mainly by interleukin-4 [18]. Thalidomide also inhibits T-cell proliferation of stimulated T-cells [19, 20].

Furthermore thalidomide modifies various integrin receptors and other surface receptors of leukocytes, including the homing receptor CD44 and the intracellular adhesion molecule 1 (ICAM-1) [21]. Thalidomide also inhibits neutrophil chemotaxis [20, 22–24]. The data about the influence of thalidomide on IFN-$\gamma$ levels are conflicting.

The most pronounced effect of thalidomide is probably its effect on tumour necrosis factor alpha (TNF-$\alpha$) production [11, 25]. Various mechanisms for the inhibition of TNF-$\alpha$ have been suggested, including accelerated degradation of TNF-$\alpha$ mRNA [26] or binding to alpha1-acid glycoprotein, which is known to have anti-TNF-$\alpha$ activity [27]. In addition thalidomide seems to block NF-$\kappa$B-activity [28]. NF-$\kappa$B is a critical transcription factor involved in immune responses and cellular growth. NF-$\kappa$B can translocate to the nucleus and regulate many genes including the TNF-$\alpha$ gene [29].

Thalidomide also inhibits IL-6, probably also by blocking NF-$\kappa$B, and IL-12 production by monocytes [30]. In contrast synthesis of IL-2 is enhanced by thalidomide [20].

Thalidomide has been described as an inhibitor of angiogenesis as early as 1994 [31], and has a strong anti-angiogenic activity in vascular endothelial growth factor (VEGF)- and basic fibroblast growth factor (bFGF)-induced angiogenesis. These anti-angiogenic effects are especially important in the treatment of diseases involving neoformation of blood vessels including most malignancies.

Adverse effects

In general the most serious adverse effects associated with thalidomide are a dose dependent reversible neuropathy and of course teratogenicity. Phocomelia of the upper extremities is the most prominent congenital defect linked to thalidomide [32]. Many other defects have been reported including congenital heart deformity, spina bifida, and other abnormalities or absence of internal organs [33]. The peripheral neuropathy induced by thalidomide is characterized as systemic peripheral
paresthesia or numbness of the feet. These symptoms are often reversible after the discontinuation of the drug. However, irreversible sensory loss has also been documented [32, 34].

The most common side effects are constipation and sedation. A dose dependency is postulated. In the last few years an enhanced incidence of deep venous thrombosis, especially in patients with multiple myeloma [35], and prostate cancer [36], who were treated with thalidomide in combination with conventional chemotherapy, has been reported. Other common side effects of thalidomide are summarized in table 1 [12, 37, 38].

**Clinical applications**

The broad indications of this drug in different diseases are not surprising because of its abundant pharmacodynamic effects.

**Erythema nodosum leprosum (ENL)**

The public health Service has overseen thalidomide in the therapy of ENL for over 20 years. ENL, a complication of leprosy, is characterized by typical painful subcutaneous nodules [39].

Many studies have reported beneficial effects of thalidomide on fever and cutaneous manifestations [40–43].

Two double blind controlled trials have evaluated the effectiveness of 100 mg thalidomide four times daily (versus Aspirin) in controlling the cutaneous manifestation of ENL. Thalidomide was observed to have a marked effect on fever and 75% of patients were reported to have had a complete skin response [39].

Because of its low adverse effects thalidomide is favoured to corticosteroids. By combining both drugs a reduction of the dose of steroids is possible [43].

**Behcet’s disease**

There are many uncontrolled studies of thalidomide in Behcet’s disease, especially with urogenital ulcers. Thalidomide was shown to be effective in mucocutaneous disease [44].

In one case thalidomide was given in colitis with giant ulcers; that were unaffected by a treatment of colchicine. After 7 days of thalidomide treatment fever and diarrhoea disappeared. In a control-colonoscopy after 4 weeks the ulcers were virtually healed [45].

There is one published randomised trial which shows a benefit for patients in both thalidomide groups (300 mg and 100 mg) versus the patients in the placebo group [46].

**Inflammatory bowel diseases**

Thalidomide decreases production of TNF-α, a proinflammatory cytokine associated with Crohn’s disease. In some small studies of thalidomide in chronically active steroid-dependent Crohn’s disease, thalidomide appears to be well tolerated and effective. Ehrenpreis treated 22 patients with M. Crohn. Fourteen patients completed the therapy over 3 months. All of them had clinical improvement, 41% were in clinical remission. Five of six patients with fistulas experienced a complete obliteration [47].

While the intensity of Crohn’s disease activity can vary spontaneously, there seems to be a strong probability that thalidomide has been helpful.

More controlled multicenter studies are necessary [47–49].

**Rheumatoid arthritis**

Dysregulation of TNF-α was thought to play a key role in rheumatoid arthritis. There are some small studies which show different results on the efficacy of treatment with thalidomide.

In one trial 7 patients of 17 achieved complete remission, 5 showed partial remission and the last 5 no improvement. Remission lasted 6 years in 1 patient, 2 years in 3, one year in 1 [50]. Another study with 10 patients observed no significant improvement in any outcome measures [51]. Only limited efficacy was noted in a non-blinded study of 12 patients treated with pentoxifylline and thalidomide in combination. The production of TNF-α was reduced, but the ratio benefit to side effects was poor [52].

**Sarcoidosis**

Since thalidomide therapy has been shown to modify granulomatous diseases such as leprosy, the indication of cutaneous sarcoidosis (Morbus Pernio) was given.

In a trial of 10 patients with chronic cutaneous sarcoidosis resistant to conventional therapy, 7 patients had a disease regression. Skin lesions were totally repressed in 3 patients, incompletely in 4 [53]. Other studies showed some efficacy as well [54, 55].

**Aphthous ulcers in HIV-Infections**

As we know, thalidomide is effective in the treatment of mucocutaneous diseases such as aph-
thous ulcers, a known problem in patients with HIV-Infection. This symptom can be really debilitating. One double blind randomised placebo-controlled study showed that thalidomide is effective in healing aphthous ulceration of the mouth and oropharynx.

There was a complete remission in 55% of the patients. Most of the other patients had also a rapid reduction of pain and burning sensation [56, 57].

Systemic lupus erythematosus

Some clinical trials support the efficacy of thalidomide as a second line treatment of cutaneous manifestations. Thalidomide should be restricted to patients who show no response to standard therapeutic regimes because of its neurotoxicity [58–60]. One study with low dose, long-term thalidomide medication suggests that peripheral neuropathy is not as common as suggested by other studies [61].

Palliative care

Thalidomide seems to be a potential medication for palliation of many symptoms. In addition to its well known effects as a sedative and antiemetic, thalidomide has antipyretic, anticholinergic and potentially analgesic effects [37]. These properties were realised in the treatment of patients with AIDS related cachexia, of patients with painful subcutaneous nodules in leprosy, and of patients with mucocutaneous ulcers in AIDS syndrome and Behcet disease. The effects might be based on the selective suppression of immune mediators such as IL-6 and TNF-α.

Haematological malignancies

In the past decades thalidomide never really disappeared from clinical haematology and oncology, because for the treatment of refractory chronic graft versus host and otherwise refractory Langerhans histiocytosis thalidomide was successfully used [62, 63]. But a true revival of thalidomide in preclinical and clinical research has only been observed when the Barlogies group reported an impressive overall response rate (ORR) of 32% in 84 patients with multiple myeloma of whom 90% had failed after an autologous stem cell transplant [64]. Meanwhile other groups have confirmed these results with an ORR of 25–45% and response duration of 9–12 months with 10–20% of the patients free of progression after 2 years [65–68]. Based on these results thalidomide has been approved by the FDA for treatment of patients with refractory multiple myeloma.

Not surprisingly patients with Waldenströms macroglobulinaemia have been studied and successfully treated with thalidomide with an ORR of 25% [69].

In plasma cell malignancies the response occurs rather rapidly in 1–2 months and dosages of 200–400 mg/day are usually sufficient. Recently it has been shown that even a dose of 50 mg/d can be sufficient in selected cases [70]. For most patients there seems to be no need to use more toxic dosages although a dose-response effect has been documented for patients with advanced myeloma and high-risk characteristics [68]. For extramedullary presentations of a true plasmacytoma or multiple myeloma patients the response rate seems to be inferior [71, 72].

So far we do not know why thalidomide is so active in these haematological malignancies. Results of measurements of microvessel density are not affected by thalidomide nor is it a predictive factor for response [64, 73]. It is hypothesized that rather immunomodulatory properties of thalidomide are responsible for the therapeutic effect in myeloma patients [74].

For clinical purposes, studies using upfront thalidomide and thalidomide in combination with other drugs such as dexamethasone and chemotherapeutic agents, i.e. anthracyclines are in progress as well as studies for patients with smouldering myeloma [38]. We have to be careful to avoid additional toxicity such as deep venous thrombosis especially in patients treated with combination therapies [75].

For the treatment of patients with myelodysplastic syndromes and myelofibrosis there are promising but not yet conclusive data but there are casuistic observations that thalidomide might also have had a detrimental effect in some patients [76, 77]. The same holds true for patients with AML where only a few patients received enough drug to be assessable for response because of progression or toxicity [78].
Non hematological neoplasia

High grade gliomas

Because of its antiangiogenic effects, one hoped that thalidomide would be very effective in these highly vascular tumors with high microvessel density such as anaplastic mixed glioma, anaplastic astrocytoma and glioblastoma multiforme. Four phase II studies with thalidomide as single agent [79–81] or in combination with conventional chemotherapy [82] have shown promising activity in patients with high-grade gliomas.

The daily administered dose of thalidomide ranged from 200 to 1200 mg [79, 81]. Partial responses ranged from 5 to 15% [79–81] in the thalidomide monotherapy group. In the combination therapy with BCNU one complete remission (3%) and 4 partial responses (10%) were registered [82]. Tumour stabilization (CR, PR, SD) could be reached in single / combination therapy in 45–47% / 58% respectively. In the combination therapy 15% of the patients suffered from a grade IV neutropenia and 9% from a grade III thrombocytopenia. Major non-haematological toxicities attributable to thalidomide were constipation and drowsiness.

Kaposi’s sarcoma

Recent data indicate that thalidomide has some activity in AIDS related Kaposi’s sarcoma. The administered doses range from 100 mg daily [83] up to 1000 mg [84] in an escalating fashion. Responses could be found in all dose levels. Overall responses (CR and PR) ranged from 17 to 40% [83, 85], whereas no complete remission was observed. Remarkably there was no haematologic toxicity. In one study 6 out of 17 patients withdrew from therapy because of toxicity [83]. Drowsiness, depression and somnolence [84, 85] were the most common side effects, whereas no constipation was seen.

Renal cell carcinoma

Up to now four phase II studies were published for this disease. Eisen et al treated 18 patients with renal cell carcinoma with 100 mg thalidomide daily [86]. Three patients (17%) had a partial response, 3 had a stable disease for 3 months or longer. Two of the responders had failed earlier immunotherapy. These patients had significant palliative benefit within 24 hours of starting thalidomide (reduced insomnia and weight loss) and objective tumour shrinkage started within 2 weeks of starting therapy, which underlines the effect of thalidomide and argues against a spontaneous regression that is seen quite often in renal cell carcinoma.

Another 3 phase II trials with high dose thalidomide (200–1200 mg) showed responses from 0% [87] up to 9% [88], disease stabilisation after 6 months varied from 26% to 32% [87, 88]. Toxicity was quite high with frequent manifestations of fatigue, constipation and lethargy. The incidence of detected neuropathy on electromyography (EMG) attained 70% at 6 months and 100% in patients on thalidomide for 12 months [89]. In conclusion high dose thalidomide cannot be recommended since the level of toxicity is too high [89]. Because disease stabilisation occurs as a part of the natural history of metastatic renal cell carcinoma, the potential benefit of thalidomide in the mean progression free survival and overall survival is still unclear. Further studies in combination with immunotherapy or conventional chemotherapy are warranted.

Prostate cancer

Figg et al. [90] conducted a randomised phase II trial to evaluate the activity of thalidomide in patients with androgen independent prostate cancer.

Patients received thalidomide 200 mg (50 patients) or 1200 mg (13 patients). All patients were required to have failed combined androgen blockage as well as antiandrogen withdrawal. A serum prostate specific antigen (PSA) decline ≥50% was noted in 18% of patients on the low dose arm (200 mg) and in none of the patients on the high dose arm. Four of the respondents had a PSA decline greater than 150 days. No patient had a response in CT scan, however two patients had one or more lesions improved as assessed by bone scan with associated clinical benefit. The most common side effects were constipation, dizziness, oedema, fatigue and neurological complications. Because preclinical studies showed an increase in PSA in androgen independent prostate cancer cell lines [91] it is believed that the magnitude of PSA decline seen in this trial equals a real response.

Docetaxel and thalidomide have both shown single agent activity in hormone refractory prostate cancer. Based on this a randomised phase II study of weekly docetaxel with or without 200 mg of thalidomide was conducted [36]. Docetaxel was given at a dose of 30 mg/m² on day 1, 8, 15 every 4 weeks. Fifty-nine patients have been enrolled in this study, 53 were evaluated. Six (35%) of the 17 patients receiving docetaxel alone had decreases in PSA levels of at least 50%. Nineteen (53%) of 36 patients in the combination arm have met this threshold. Eight of 39 patients in the combination arm have developed a venous thromboembolism, none of them being life threatening. These data are encouraging and have to be validated through further phase II or III studies.

Malignant melanoma

Reported experience with single agent thalidomide is limited in melanoma. Eisen et al. [86] treated 17 patients with advanced melanoma with low dose thalidomide (100 mg daily). No objective response was observed, but 4 patients had stable disease for up to 5 months.

A phase I study [92] showed that temozolomide could be safely given on a continuous daily
Table 2
Results of selected published trials using thalidomide for nonhaematologic tumours.

<table>
<thead>
<tr>
<th>Tumour entity</th>
<th>patients number</th>
<th>kind of therapy</th>
<th>dose of thalidomide</th>
<th>tumour stabilisation (CR+PR+SD)</th>
<th>response rate (CR+PR)</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td>High grade gliomas</td>
<td>39</td>
<td>phase II single agent</td>
<td>800–1200 mg</td>
<td>45%</td>
<td>6% [79]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>phase II single agent</td>
<td>100–500 mg</td>
<td>47%</td>
<td>5% [80]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>phase II single agent</td>
<td>100–500 mg</td>
<td>47%</td>
<td>15% [81]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>BCNU plus thalidomide</td>
<td>800 mg</td>
<td>58%</td>
<td>13% [82]</td>
<td></td>
</tr>
<tr>
<td>Kaposis sarcoma</td>
<td>17</td>
<td>phase II single agent</td>
<td>100 mg</td>
<td>na</td>
<td>35% [83]</td>
<td></td>
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<td></td>
<td>20</td>
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<td>200–1000 mg</td>
<td>na</td>
<td>40% [84]</td>
<td></td>
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<tr>
<td></td>
<td>28</td>
<td>phase II single agent</td>
<td>200 mg vs 800–1200 mg</td>
<td>7%/-0%</td>
<td>0% [101]</td>
<td></td>
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<td>Breast cancer</td>
<td>12</td>
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<td>100 mg</td>
<td>0%</td>
<td>0% [86]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>phase II single agent</td>
<td>200 mg</td>
<td>47%</td>
<td>15% [81]</td>
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<tr>
<td></td>
<td>40</td>
<td>BCNU plus thalidomide</td>
<td>800 mg</td>
<td>58%</td>
<td>13% [82]</td>
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<tr>
<td>Ovarian cancer</td>
<td>19</td>
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<td>100 mg</td>
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<td>0% [102]</td>
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<td>NSCLC</td>
<td>9</td>
<td>carboplatin/taxol/thalidomide</td>
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<td>escalation fashion</td>
<td>na</td>
<td>0% [103]</td>
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<td>Renal cell carcinoma</td>
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<td>100 mg</td>
<td>34%</td>
<td>17% [86]</td>
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<tr>
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<td>41%</td>
<td>9% [88]</td>
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<td>28%</td>
<td>5% [89]</td>
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<tr>
<td>Prostate cancer</td>
<td>63</td>
<td>phase II single agent</td>
<td>Randomised 200 vs 1200 mg</td>
<td>27% *</td>
<td>18%/-0% [90]</td>
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<td></td>
<td>59</td>
<td>docetaxel plus/minus thalidomide</td>
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<td>na</td>
<td>53%/35% [91]</td>
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<td>Malignant melanoma</td>
<td>17</td>
<td>phase II single agent</td>
<td>100 mg</td>
<td>0%</td>
<td>6% [86]</td>
<td></td>
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<tr>
<td></td>
<td>12</td>
<td>phase I temozolomide plus thalidomide</td>
<td>100–400 mg</td>
<td>na</td>
<td>42% [92]</td>
<td></td>
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<tr>
<td></td>
<td>10</td>
<td>phase II DTIC plus thalidomide</td>
<td>200–400 mg</td>
<td>40%</td>
<td>30% [94]</td>
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<tr>
<td>Hepatocellular cancer</td>
<td>23</td>
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<td>100–800 mg</td>
<td>45%</td>
<td>9% [104]</td>
<td></td>
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<tr>
<td></td>
<td>27</td>
<td>phase II single agent</td>
<td>200–800 mg</td>
<td>7%</td>
<td>3% [95]</td>
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<tr>
<td>Malignant mesothelioma</td>
<td>15</td>
<td>phase II randomised study cisplatin/gemcitabine/thalidomide vs thalidomide alone</td>
<td>100–500 mg</td>
<td>55%/50%</td>
<td>0%/0% [97]</td>
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<tr>
<td>Metastatic neuroendocrine tumours</td>
<td>18</td>
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<td>400 mg</td>
<td>78%</td>
<td>0% [96]</td>
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</table>

na: not applicable
*: cumulative in high and low dose arm

Schedule with thalidomide to patients with metastatic melanoma. Based on this, two phase II studies were conducted. Hwu et al. [93] treated 12 patients with different temozolomide doses, and schedule groups in combination with thalidomide at a dose of 200 or 400 mg. Five major responses (one complete, four partial) were observed at the higher temozolomide dose levels. The median duration of response was 6 months; the median survival rate was 12.3 months. In the other study DTIC was combined with thalidomide in escalating doses [94]. Ten patients were enrolled, 5 had had prior adjuvant vaccine or immunotherapy. DTIC was given at a dose of 1000 mg/m² every 3 weeks, the starting dose of thalidomide was 200 mg daily by oral route. Doses were escalated every 3 weeks. The median tolerated dose was 200 mg. Three out of 10 patients had a partial response, one patient had stable disease. Responses were seen in skin, retroperitoneal lymph nodes, lung and liver metastases. Toxicity from thalidomide was severe constipation, peripheral neuropathy, fatigue and pedal oedema. In conclusion it can be postulated that the combination therapy is well tolerated and further phase II/III evaluation is warranted.
Other tumor types

Thalidomide is used in many phase II studies in different solid tumors, such as hepatoma [95], neuroendocrine tumors [96] and mesothelioma [97, 98]. Thalidomide is also use in colorectal cancer normally in combination with irinotecan. In this combination, thalidomide is able to reduce the irinotecan associated late-onset diarrhoea and allows the continuation of otherwise not applicable chemotherapy with irinotecan [99, 100]. However the mechanisms by which thalidomide eliminates the gastrointestinal toxic effect of irinotecan are still unclear.

Overview

In table 2 results of selected published trials using thalidomide for nonhaematologic tumours are summarised. It is important to state that up to now the use of thalidomide outside of clinical trials cannot be recommended for nonhaematological malignancies.

Ongoing studies

The best combination therapy and type of action in multiple neoplasias are still unknown. Further investigation is necessary. Under the regimen of the National Cancer Institute 39 phase I/II and III studies are ongoing. In Switzerland two phase II studies are currently ongoing, one in melanoma and one in prostate cancer, another trial for renal cell carcinoma is planned. A summary is given in table 3.

Future directions

There are now many options to use thalidomide in patients with haematological and non-haematological malignancies and in patients with non malignant diseases, but we need prospective randomised trials in order to evaluate the best regime for individual patients in the future.

Furthermore, thalidomide analogues such as CC-5013 with a more favourable preclinical toxicity and activity profile than thalidomide are now tested in phase I trials.

Many different pathways in the angiogenesis are targeted by highly selective drugs as shown below.

SU 5416 (Semaxanib) works as a selective inhibitor of the tyrosine kinase activity of Flk-1/KDR, a vascular endothelial growth factor (VEGF) receptor. Other drugs (Bevacizumab) work by neutralising the activity of VEGF. The exact mechanism of action of many other antiangiogenic drugs (i.e. thrombospondin-1, squalamine, TNP-470, NM-3) is not yet clearly defined and should be targeted in future research.

In conclusion, thalidomide banned in the sixties from the market because of its toxicity is nowadays the first antiangiogenic drug that is used routinely and with success in the clinics. But hopefully this is only the beginning of the development of a wholly new therapeutic modality that could change the course of many diseases for which at the moment only limited treatment options exist.

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<table>
<thead>
<tr>
<th>Kind of tumour</th>
<th>therapy regimen</th>
<th>study phase</th>
<th>study number</th>
</tr>
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<tr>
<td>Malignant glioma</td>
<td>topotecan and thalidomide</td>
<td>phase I</td>
<td>NCI-V01–1651, RUSH-G101</td>
</tr>
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<td>Metastatic melanoma</td>
<td>temozolomide and thalidomide</td>
<td>phase I/II</td>
<td>MSKCC-99103, NCI-G00–1786</td>
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<tr>
<td>Myelofibrosis</td>
<td>thalidomide</td>
<td>phase II</td>
<td>NCCITG-N9982</td>
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