Phase II trial of thalidomide in renal-cell carcinoma

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Introduction

Metastatic renal cell carcinoma (RCC) is refractory to chemotherapy and median survival has been reported to range from 2 to 12 months [1–3]. Since the early 1980s, both α-interferon (IFN) and interleukin (IL)-2 have demonstrated some activity, both alone or combined, with objective response rates ranging from 5% to 40% [4–8]. However, although these cytokines are the only licensed drugs in Europe for RCC, the benefit of this treatment remains questionable and novel drugs are urgently needed. Chemotherapy has been studied extensively but to date, no drug has proven efficient [9].

During the last 10 years, angiogenesis has been recognized as a key factor in tumor progression [10] and has thus become a new target for anti-neoplastic drugs, many of which are currently under investigation. Thalidomide, initially marketed as a sedative in the 1950s, is known to elicit potent anti-angiogenic activity. It was first postulated that the teratogenicity it induced was due to the inhibition of blood vessels in the developing limb bud [11]. Subsequently, thalidomide demonstrated a capacity to eradicate experimental tumors in mice [12], to induce apoptosis of neovasculature established in experimental models [13] and to treat Kaposi’s sarcoma, a vascular tumor [14].

These observations prompted investigational studies on thalidomide in several malignant diseases. Multiple myeloma was the first disease where its activity was clearly demonstrated [15]. Solid tumors also proved to be a good target, and many phase II trials are ongoing. Promising preliminary results have been reported in RCC [16, 17], and this provided the impetus for the phase II study reported here.
adequate contraception; patients were fully informed about the teratogenicity of the drug.

Treatment plan

Thalidomide was supplied in 100 mg capsules (Laphal, Allauch, France), and was administered nightly at 400 mg. The dose was increased to 800 mg after 6 weeks if disease was overtly progressive or after 12 weeks in the absence of an objective response. In patients whose disease continued to progress after 6 or 12 weeks at 800 mg, the dose was increased to 1200 mg if tolerated. Treatment was stopped if disease continued to progress after a minimum of 6 weeks at 1200 mg, but not before 3 months unless toxicity was unacceptable.

Follow-up schedule

Clinical and biological toxicities were evaluated after 2 weeks, 6 weeks and then every 6 weeks after the initiation of treatment.

Fatigue was scored on a 0 to 100 visual analogical scale.

Electromyography (EMG) was performed in every patient at baseline, and after 6 and 12 months in patients who were still on therapy. Neuro-pathy was classified as severe when a decrease in the amplitude of sensory nerve action potentials was observed both in the lower and upper limbs, as moderate if this decrease was only observed in the lower limbs, and as absent or mild if there was no decrease in amplitude or if such a decrease was restricted to the distal part of the limb.

Response assessment

Standard WHO response criteria were used. Complete response (CR) was defined as the absence of all clinical evidence of disease, partial response (PR) as a ≥50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions for at least 1 month, and stable disease (SD) as a decrease of <50% or an increase of <25%. Progressive disease (PD) was, as usual, defined as an increase of ≥25% in the sum of the products of the perpendicular diameters of all measurable lesions, or the appearance of any new lesion. An objective response (OR) was defined as a CR or a PR.

Response was assessed every 12 weeks on thoracic and abdominal dynamic computed tomography (CT) scans: helical CT scan (High speed-CTi; GE Medical Systems, Milwaukee, WI) was first performed without contrast injection in order to locate the lesions requiring measurement, then after a bolus injection of contrast to assess any increase in densities [total dose 140 ml of non-ionic agent (Ultravist370®; Schering, Berlin, Germany), flow rate 3 ml/s, scan delay 40 s]. The size and density of lesions were measured. Two orthogonal diameters were required to determine the size of the lesions. Density measurements (Hounsfield unit) were obtained by mapping the region of interest on each lesion before and after contrast injection. The difference between density values before and after contrast injection was calculated to assess changes in lesion vascularity during treatment.

The duration of response was measured from the date of documented response and survival from the date of entry into the study.

Ancillary studies

Color Doppler ultrasonography was used to assess tumor vascularity in patients whose tumor was accessible to ultrasound. Ultrasonography was performed at baseline and then every 6 weeks throughout the treatment. Images were obtained with a digital Toshiba Power-Vision 8000 Doppler ultrasonograph (Toshiba, Nasu, Japan). The three largest diameters were used to calculate the volume of each target lesion and angiogenesis and necrosis were evaluated as follows.

- Semi-quantitative evaluation of the flow rates (from 0 to 3+) according to the number of vessels visualized (0, 1–5 = +, 6–10 = ++, >10 = +++).
- Quantification of feeding arteries: 0, 1–5, 6–10, >10.
- Necrosis from 0 to 2: absent (0), <50% (1) and ≥50% (2).

Serum levels of cytokines involved in angiogenesis [vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), IL-12 and tumor necrosis factor (TNF-α)] were measured at baseline, and at weeks 6, 12, 18 and 24. Cytokine measurements were performed using ELISA kits: VEGF and FGF basic kits were purchased from R&D Systems (Minneapolis, MN, USA), heterodimeric IL-12 (p70) and TNF-α from Immunotech (Marseille, France) with a sensitivity threshold of 5, 3, 5 and 5 pg/ml, respectively. Standard curves were derived for each assay from duplicate samples and experimental values were computed using linear regression analysis.

Statistical analysis

The purpose of this phase II study was to assess the OR rate at 6 months. Patients were accrued using a two-stage phase II design [18]. An OR rate >20% was required to conclude that thalidomide was effective and <5% to conclude that it was inactive. Twenty-two patients had to be enrolled during the first stage of the study. If less than two ORs were observed, no further patients would be accrued; if two or more ORs were observed, 18 additional patients were to be included. Based on these 40 patients, thalidomide would be considered ineffective if less than four ORs were observed and effective if five or more were observed (type I error = 0.05, power = 90%). However, due to the rapid accrual during the study and the encouraging preliminary results from phase I [16], the design was further modified to enroll the 40 patients at one time.

Results

Patient demographics

Forty patients were treated for metastatic RCC at the Institut Gustave Roussy from January to June 2000. Table 1 lists patient characteristics. The median age was 61 years. Most of the patients (80%) had undergone nephrectomy. All but six patients had previously received immunotherapy. The six patients who received thalidomide as first-line treatment belong to the subgroup of patients with a particularly poor likelihood of responding to immuno-therapy, i.e. patients with more than one metastatic site including the liver and an interval of <1 year between the primary tumor and metastases [5].

As a whole, this patient population carried a poor prognosis: the majority of them (78%) had three or more metastatic sites, and 21 (53%) had previously received two or more lines of medical treatment.
Dose adaptation

All patients started thalidomide at 400 mg. At week 6, four patients stopped treatment because of toxicity, 28 remained at 400 mg, seven had their dose increased to 800 mg because of obvious PD, and the dose was decreased to 200 mg in one patient because of severe neuropathy (it was finally stopped 2 weeks later).

At week 12, 31 patients were still on therapy: two at 400 mg, 26 at 800 mg and three had a further 400 mg dose increment from 800 to 1200 mg. At week 18, 25 patients were still on thalidomide at 800 or 1200 mg (17 and eight patients, respectively). At week 24, 17 patients continued treatment at 800 or 1200 mg (four and 13, respectively). Finally, at 9 months, only eight patients (two at 800 and six at 1200 mg) were still on study therapy, but all these patients stopped treatment after 1 year because of severe neuropathy diagnosed by EMG.

Response to treatment and survival

The two stages of this phase II trial were not analyzed because all 40 patients had been enrolled before the assessment of response at 6 months of the first 18 patients became available. Table 2 shows response to study treatment. No OR was observed at 12 weeks, but disease was stable in 11 patients. At 6 months, two patients achieved a PR, corresponding to an OR rate of 5%. One of them had lung and bone metastases and the other patient had lung metastases and a large inguinal mass. These two PRs lasted 3 and 5 months, respectively. Nine patients had SD, with a 40% decrease in the local recurrence, which continued to shrink after 8 months in one of them. Finally, disease stabilization was achieved in seven patients after 1 year.

Figure 1 shows overall survival. The 1 year survival rate was 38% (95% CI 24% to 55%) and the median survival time was 10 months.

Toxicity

No biological toxicity was reported.

One unexpected death occurred after 26 days of treatment. This patient, who was in perfect condition at week 2, was hospitalized in the intensive care unit at day 26 because of septic shock, related to *Bacteroides fragilis* septicemia; she died of multiorgan failure, without evidence of the etiology of...
septicemia. An autopsy was refused. Although a connection with the thalidomide treatment remains uncertain, it cannot be totally excluded.

Table 3 lists the clinical toxicities observed during therapy in the remaining 39 patients. Fatigue was a common toxicity; Figure 2 better illustrates an increasing analogic scale with time on therapy. Neurological toxicity was substantial. Lethargy was frequent, and occurred from the beginning of treatment. In some patients, lethargy was severe, with confusion in some patients to such an extent that treatment had to stopped. Thus, three patients, on a dose of 400 mg, had treatment interrupted after 6 weeks because of grade 3 (two patients) or 4 (one patient) central neurotoxicity.

Peripheral neuropathy was also very common. The rates of moderate (20%) and severe (15%) neuropathy diagnosed on EMG at baseline (40 patients) increased to 40% and 30%, respectively, at 6 months (20 patients). In addition, among the six patients who had an EMG after 1 year, all but one had severe neuropathy.

Thromboembolism was another unexpected toxicity. Nine patients experienced such toxicity during the first 12 weeks of treatment: six patients had deep vein thrombosis in the leg and three patients had vena cava thrombosis. Of these nine patients, three developed pulmonary embolism, requiring transfer to the intensive care unit for one patient. All these patients improved with heparin treatment, and thalidomide was continued in all nine.

Dynamic CT scan

During treatment, changes in density values after contrast injection were not significant compared with the clinical status of patients. At baseline, increased density after contrast injection had no predictive value compared with response to treatment and the survival rate. Table 4 summarizes the data on modifications of baseline density values after 12 and 24 weeks of treatment.

Doppler ultrasound

Changes in the vascularization of target lesions were observed in some patients. Table 5 summarizes data on vascularization, necrosis and tumor volume at baseline and after 6 weeks. No significant changes were observed, and neither response to treatment (PD versus SD or OR) nor survival differed according to changes in vascularization or necrosis.

Cytokine levels

Figure 3 details the results of VEGF, basic FGF, IL-12 and TNF-α measurements at baseline, and at weeks 6, 12, 18 and 24. None of these cytokines was predictive of survival at baseline, and no significant changes were observed in them during therapy.

Discussion

We observed two PRs and nine SDs after 6 months of treatment in this trial. Although our response rate (5%) is lower than the initial response rate reported by Amato [16] using the same schedule in a phase I study, or the three PR in 18 treated patients reported by Eisen et al. [17] using lower doses (100 mg daily), it is within the range recently reported by the MD Anderson Cancer Center in a larger study [22]. Encouraging disease stabilization was also observed in patients who had PD at study entry, but the benefit of such SD remains questionable. Moreover, the accuracy of tumor response assessment in RCC is still difficult [23]. Notwithstanding, the overall survival rate of our patients is acceptable, with a 1 year survival rate of 38% (range 24–55%) and a median survival time of 10 months.

The precise mechanism of thalidomide anti-tumor activity remains obscure. Serial measurements of serum VEGF, basic FGF, IL-12 and TNF-α did not reveal any distinct effect attributable to thalidomide. None of these cytokines was

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Table 3. Clinical toxicity (in 39 patients); maximal grade is given for all patients on thalidomide for 6 weeks

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (41)</td>
<td>13 (33)</td>
<td>9 (23)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>13 (33)</td>
<td>14 (36)</td>
<td>5 (13)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Neuropathya</td>
<td>7 (18)</td>
<td>3 (8)</td>
<td>3 (8)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (21)</td>
<td>13 (33)</td>
<td>3 (8)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (8)</td>
<td>2 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>6 (15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>5 (13)</td>
<td>3 (8)</td>
<td>1 (3)</td>
<td></td>
</tr>
</tbody>
</table>

*aNeuropathy assessed by clinical examination.*
predictive of response to treatment or survival. Similarly, despite some changes in tumor vascularization and necrosis seen on color Doppler ultrasound, none of them was related to further tumor response (or stabilization), or to overall survival. Dynamic CT scan has also demonstrated its ability to detect tumor hypervascularization during the early phase of contrast injection (acquisition time <1 min after bolus injection) in several studies in the literature [24]. However, as in the case of color Doppler ultrasound, statistical analysis of our data showed no predictive value of dynamic CT scan findings, either in terms of either response to treatment or survival. The lack of such surrogate markers predictive of the efficacy of thalidomide remains a key problem for all the anti-angiogenic drugs currently under investigation [25, 26].

Toxicity induced by thalidomide was greater in magnitude in our hands than that reported by previous investigators. Fatigue, constipation and lethargy were common, and undoubtedly impaired the quality of life of our patients.

Table 4. Dynamic CT scan data

<table>
<thead>
<tr>
<th>Patient status</th>
<th>PR and SD [median (range)]</th>
<th>PD and DP [median (range)]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDL baseline (n = 40)</td>
<td>55 (11 to 109)</td>
<td>48 (10 to 113)</td>
<td>0.63</td>
</tr>
<tr>
<td>VDDL (%) 12 weeks (n = 33)</td>
<td>2 (–63 to +326)</td>
<td>11 (–61 to +390)</td>
<td>0.95</td>
</tr>
<tr>
<td>VDDL (%) 24 weeks (n = 19)</td>
<td>–13 (–63 to +71)</td>
<td>–13 (–60 to +59)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

DDL, difference between density levels before and after contrast injection; VDDL, variation in DDL after 2 and 24 weeks of treatment; PR, partial remission; SD, stable disease; PD, progressive disease; DP, death of the patient.

Table 5. Doppler ultrasound data

<table>
<thead>
<tr>
<th>Ultrasound data</th>
<th>Baseline (n = 28) [median (range)]</th>
<th>Week 6 (n = 26) [median (range)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascularization</td>
<td>2 (0–3)</td>
<td>1.5 (0–3)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>0 (0–2)</td>
<td>0.4 (0–2)</td>
</tr>
<tr>
<td>Volume</td>
<td>225 (1–2944)</td>
<td>196 (1–2816)</td>
</tr>
</tbody>
</table>

Figure 3. Cytokine levels before and during therapy. (A) VEGF; (B) basic FGF; (C) IL-12; (D) TNF-α.
analogic scale demonstrated a very high fatigue score in most of our patients, with a median score rising from 30 to 80 at 6 months. Neuropathy was definitively a dose-limiting toxicity for long-term use of the drug. In our series, electrophysiological studies showed that the incidence of moderate or severe neuropathy was 70% after 6 months, and that all the patients developed severe neuropathy after 1 year of therapy. This incidence is much higher than the two cases of grade 2 neuropathy reported by Eisen et al. [17]. One of the reasons is certainly the higher doses of thalidomide used in our study, since neuropathy appears to be dose dependent [27]. Another important reason is that EMG was used to monitor all our patients at baseline and after 6 months of treatment, thus allowing better detection of neuropathy than clinical examination.

The extent to which thromboembolism occurred in our study was unforeseen. Venous thrombosis is a common feature during cancer, so we did not consider it mandatory to stop thalidomide at initial onset in our patients. However, the incidence of this complication in this series was much higher than in any phase II clinical trial of RCC reported to date, and this led us to conclude that thalidomide was directly responsible for these thromboembolic events, as also recently reported in patients with multiple myeloma [28]. The mechanism by which thalidomide promotes venous thromboembolism remains obscure. We performed serial blood tests to check hemostasis in 15 consecutive patients in this trial (data not shown), but none of these tests was abnormal during treatment. Given the frequency of this side-effect in patients receiving thalidomide, far more caution is recommended. Based on our experience, thalidomide could probably be continued under anti-coagulant therapy without impairment of thromboembolic disease.

Our findings suggest that thalidomide has marginal activity tainted by high toxicity in RCC. This drug should therefore not be considered as standard treatment in RCC, at least not with this high-dose schedule. Whether lower doses, or combined treatment with cytokines, might prove beneficial to patients remains questionable.

Acknowledgements

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References