Low-dose Thalidomide in patients with Metastatic Renal Cell Carcinoma

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Abstract

Objective: To evaluate the role of thalidomide in patients with metastic renal cell carcinoma and the efficacy, toxicity and response rates to thalidomide.

Methods: The phase-II clinical trial study was conducted at the Sindh Institute of Urology and Transplantation (SIUT), Karachi between November 2008, and April 2009, comprising 80 patients with metastic renal cell carcinoma who had either progressed on or were not suitable for immunotherapy/biologic therapy. After institutional approval and informed consent, the patients received thalidomide 400mg daily. Thalidomide was continued until the time of disease progression or documented severe toxicity. Primary endpoints were the safety, response, progression free survival (PFS) and overall survival (OS). SPSS version 16.0 was used for statistical analysis.

Results: The median follow-up was 18 months (15-20); median age was 51.11 years (range 23-73). Three were 59 (73.8%) males. The bone (n=83; 47.5%), lungs (n=26; 32.5%) and lymph nodes (n=8; 10%) were frequent sites of distant metastases. Of the patients, 32 (40%) had previous different systemic treatments. Grade 3 and 4 toxicities were; fatigue (n=34; 42.5%), sensory neuropathy (n=8; 10%), deep venous thrombosis (n=7; 8.8%) and gastrointestinal upset (n=6; 7.5%). Response rates were available for 75 patients: partial 48 (60%); stable disease 12 (15%); progression 15 (18.8%); while 5 (6.2%) were not evaluated. Median progression free survival and overall survival rates were 7 months and 19 months respectively.

Conclusion: Low-dose thalidomide resulted in manageable toxicity, better response rates, progression free survival and overall survival in the study population. Further large randomised trials are warranted.

Keywords: Metastatic renal cell carcinoma, Thalidomide, Anti-angiogenesis, Pakistan. (JPMA 62: 876; 2012)

Introduction

Thalidomide was introduced into clinical practice in the 1950s as sedative agent but withdrawn when its severe teratogenecity (Phocomelia and Amelia) was discovered.[1] Later on in the early 1990s it was postulated that thalidomide-induced teratogenicity was due to the inhibition of blood vessels in the developing limb buds during embryonic life.[2] Following extensive pre-clinical studies of the anti-angiogenesis inhibitor effects of thalidomide, this drug was approved by the Food and Drug Administration in 1998 for use in erythema nodosum leprosum.[3] Subsequently, its anti-angiogenic effects were seen in various haematological malignancies (multiple myeloma, Waldenstrom's macroglobulinaemia, kaposi sarcoma) and solid tumours (hormone refractory prostate cancer, glioma and renal cell carcinoma).[4-6]

Renal cell carcinoma (RCC) of kidney usually demonstrates mutations or deletions in the Von Hippel Lindau (VHL) gene, which results in over-expression of vascular endothelial growth factor (VEGF) and increased vascularity.[7] Although precise mechanism of action of thalidomide as cancer therapy is not known, but available data has shown that its molecular effects apart from VEGF inhibition are mediated through (a) down-regulation of cell surface adhesion receptors,[8] (b) degradation of messenger ribonvcleic acid (mRNA) of tissue necrosis factor alpha (TNF-α) and fibroblast growth factor (FGF),[9] (c) binding of growth factor promoter sites in DNA,[10] and (d) DNA damage by hydroxyl free radicals.[11]

The burden of RCC is increasing across the world, including Pakistan.[12] Our phase-I trial had showed that metastatic renal cell carcinoma (mRCC) was the third commonest urologic malignancy in our hospital following bladder and prostate cancers.[13] Debulking nephrectomy and immunotherapy are still the common treatments for such patients. The tyrosine kinase enzyme, VEGF and Mammalian target of Rapamycin (mTOR) inhibitors are very expensive systemic therapy options with less promising results.[14]

We prospectively investigated the impact of low dose

thalidomide on tumour response, progression free survival (PFS) and overall survival (OS) rates and its efficacy, tolerance and safety profile in Pakistani patients with mRCC.

Patients and Methods

Between November 2008 and April 2009, 80 patients with mRCC were enrolled in this phase-II trial after approval from the institutional ethical committee. All patients gave informed consent and were followed until time of progression (July 2010). Those who were enrolled were patients of histopathologically confirmed mRCC; patients who were either not suitable for or progressed on immunotherapy, hormonal therapy or biologic therapy; measureable disease on computed tomography (CT) or magnetic resonance imaging (MRI); and normal haematological, chemistry, liver and renal functions. Those excluded were patients with documented brain metastasis, pregnancy and life expectancy <3 months.

All patients started thalidomide at dose of 400mg daily. Thalidomide was supplied in 100mg capsules (Thalido, ATCO Laboratories Pakistan®). No dose escalation was suggested. The drug was stopped if the disease progressed after a period of 8 weeks of starting the drug, or immediately if patients experienced unacceptable toxicity.

Adverse events were graded according to the National Cancer Institute's Common Toxicity Criteria (CTC) version 2.0; fatigue was scored on 0-100 visual scale and was recorded during follow-up initially twice weekly for 3 months then on a monthly basis. Haematology and serum chemistry were checked on a monthly basis.

Response evaluation criteria in solid tumours (RECIST) were also used.[15] Complete response (CR) was defined as disappearance of all known lesion(s) confirmed at 4 weeks; partial response (PR) as at least 30% decrease confirmed at 4 weeks; stable disease (SD) as neither PR nor PD criteria met and progressive disease (PD) as 20% increase or no CR, PR, or SD documented before increased disease, or appearance of any new lesion(s). An objective response was defined as a CR or PR.

The response was evaluated at every 8 weeks by CT chest; abdomen and pelvis, using contrast enhanced images on helical CT scannerEmotions 6 Siemens®. Hounsfield units were obtained by selecting the region of interest (ROI) on each lesion before and after contrast administration. Bi-dimensional measurements were required to determine the size of lesions.

The objective response (OR) was a binary variable and was scored as 0 or 1 based on achieving presence of CR or PR. The study design was planned using Simon's optimal two-stage design,[16] according to which, to achieve a response rate of 15% to thalidomide, minimum 40 patients with 70% power and 95% confidence interval (95% CI) were required. Additional accrual of patients was decided upon response rates and investigators' approval.The descriptive data (mean, median, range and frequency) were calculated using SPSS version 16.0. The response rates and toxicities were summarised with 95% confidence intervals (95% CI). PFS and OS were calculated using the Kaplan Meier method.

Results

The mean age of patients was 51.11±23 years (range 23-73). Of the total, 48 (60%) had undergone previous nephrectomy. The majority of patients (n=52; 65%) had good performance status of 1-2 and majority (n=54; 67.5%) had poor Memorial Sloan-Kettering Cancer Centre (MSKCC) score. The bone (n=38; 47.5%), lungs (n=26; 32.5%) and para-aortic lymph nodes (n=8; 10%) were frequent sites of distant metastasis (Table).

Table: Patient Characteristics.

Variables	Number of patients
Mean age (years) SD±23	51.11 (range 23-73)
Gender	
Male	59 (73.8%)
Female	21 (26.2%)
Location of primary	
Right	47 (58.8%)
Left	33 (41.2%)
ECOG Performance Scale	
0	13 (16.2%)
2-Jan	52 (65.0%)
4-Mar	15 (18.8%)
Number of Metastitic sites	
1	0
2	6 (7.5%)
3	10 (12.5%)
4	47 (58.8%)
5 or more	17 (21.2%)
Metastatic sites	
Para-aortic lymph nodes	8 (10.0%)
Bones	38 (47.5%)
Lungs	26 (32.5%)
Brain	3 (3.75%)
Mediastinal lymph nodes	2 (2.50%)
Others	3 (3.75%)
Previous treatments	
Nephrectomy	48 (60.0%)
Radiation therapy	12 (15.0%)
Immunotherapy	18 (22.5%)
Hormonal therapy	2 (2.50%)
Suppotiveand combination treatments	
Bisphosphonates	30 (37.5%)
More than two treatments (excluding nephrectomy)	50 (62.5%)
MSKCC risk score	
Favorable	1 (1.30%)
Intermediate	25 (31.2%)
Poor	54 (67.5%)

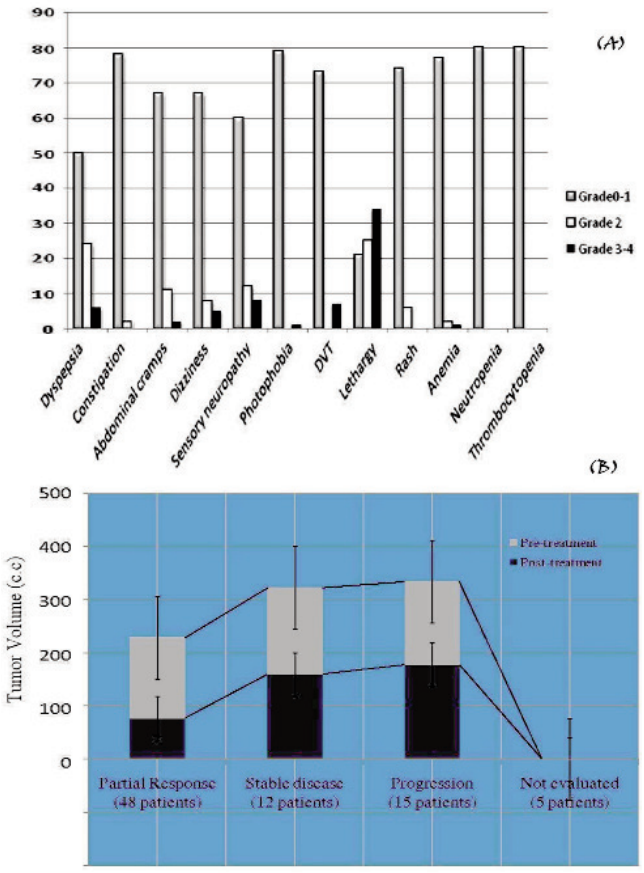

Figure-1: (a) Toxicity profile of thalidomide 400mg at the time of analysis, (b) Pre-treatment and post-treatment tumour volume reduction (response evaluation).

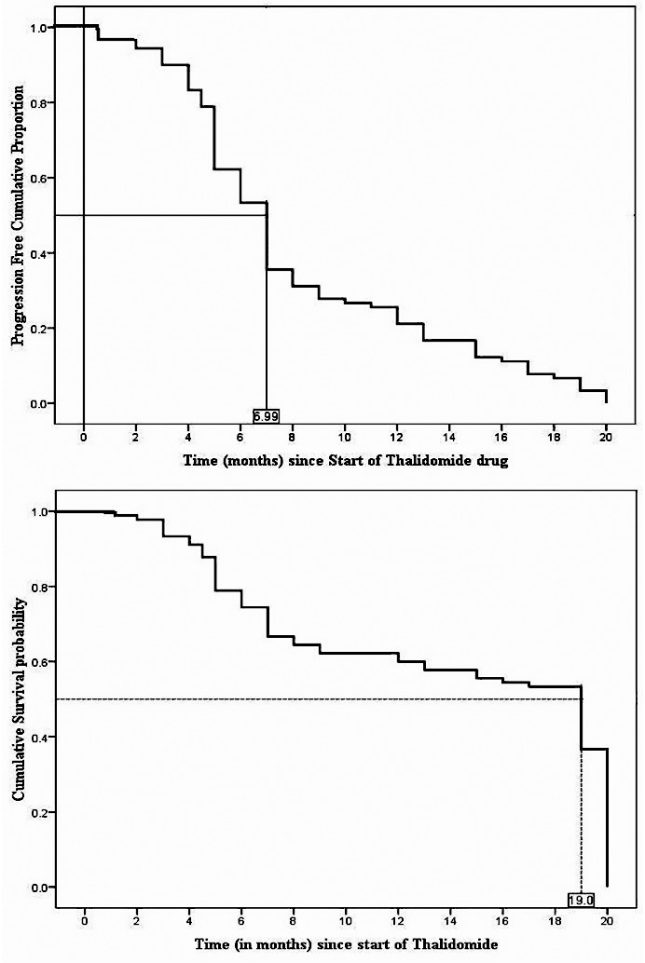

Figure-2: (a) Progression-free survival; and (b) overall survival in patients receiving low-dose thalidomide.

The most common grade 3 and grade 4 side effects seen were lethargy (n=34; 42.5%), sensory neuropathy (n=8; 10%), dizziness (n=6; 7.5%), abdominal cramps and dyspepsia (n=6; 7.5%) (Figure-1a). No severe haematological toxicity, especially febrile neutropenia, was noticed secondary to thalidomide. Seven patients (8.8%) experienced deep venous thrombosis (DVT) at 6 months of thalidomide. No treatment-related death was seen. The dose was reduced to 300mg in 21 (26.2%) patients with severe sensory neuropathy and gastrointestinal upset, until the side effects were resolved. At 6 months, 50 (62.5%) patients continued thalidomide with dose 400mg daily, and at one year only 24 (30%) patients were continued on the dose.

At 6 months, response rates were available for 75 patients. No patient achieved CR; 38 (47.5%) achieved PR; 12 (15%) had SD; and 15 (18.8%) patients had PD (Figure-1 b). At one year, 10 (12.5%) patients achieved PR; 14 (17.5%) had SD; and 25 (31.2%) patients had PD. At one year, OR was reduced from 47.5% at 6 months to 12.5%. Among the patients who had PR, the median time to response was 70 days (50 - 120) and the median duration of response was 80 days (30-120).

The combined median PFS and OS were 7 months and 19 months respectively. The one-year survival rate was 61% (95% CI 26-74) (Figure-2 a and b).

Discussion

With low-dose thalidomide of 400mg daily, we observed 38 (47.5%) PRs and 12 (15%) SDs after 6 months, and by the completion of one year, 10 (12.5%) PRs and 14 (17.5%) SDs were achieved. The objective response of our study was 47.5% at 6 months which dropped to 12.5% at one year. The reason for better response rates could be justified by incorporating low drug doses, better compliance, lesser side effects and more patients available for response evaluation as compared to other similar studies of high-dose thalidomide in mRCC.[17,18] Similar to our study, low-dose thalidomide (100mg) was also used by Eisen et al in 18 patients with mRCC and they found PR in 17% cases and median PFS was >3 months.[19] Further, the SDs were less observed in our study

compared to other studies. The stabilisation of disease has been a recognised feature of the natural history of RCC,[20] but it is less likely to occur in our patients who were on low-dose thalidomide.

The lethargy, sensory neuropathy and GI upset were common expected side effects in our patients. Criticism may arise for not doing electromyography (EMG) in our patients for the evaluation of sensory neuropathy, and grading was performed on the basis of subjective complaints and clinical examination. This could be the cause of reporting less sensory neuropathies as compared to other similar trials. Seven (8.8%) patients experienced DVT at 6 months of low-dose thalidomide. We believe that the incidence of this unexpected toxicity was much higher as reported in other studies excluding the study by Escudier et al, who reported 15% DVT in their mRCC patients.[21] Based on our experience, we recommend anticoagulation prophylaxis for patients receiving low-dose thalidomide. International Myeloma Working Group (IMWG) has also recommended aspirin for patients with one risk factor for venous thromboembolism (VTE), and low molecular weight heparinoid (LMWH equivalent to enoxaparin 40mg per day) for two or more risk factors in myeloma patients receiving thalidomide.[22] No treatment-related death was observed in the study.

The median PFS and OS data of the study was comparable with the results of trials which incorporated sorafenib and temsirolimus in mRCC patients.[23,24] However, our results were inferior as compared to sunitinib which is the first-line recommended drug for patients with mRCC.[25]

Conclusion

Thalidomide can be offered to patients with mRCC who are not suitable for sunitinib. Further large randomised trials are required to explore the potential anti-angiogenic and immunomodulatory effects of thalidomide in mRCC as a monotherapy or in combination.

Acknowledgement

Authors dedicate this study to Professor Adibul Hasan Rizvi, Director Sindh Institute of Urology & Transplantation (SIUT), Karachi, Pakistan for his services to poor cancer patients.

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