

Review

Treatment Options in Metastatic Renal Cell Carcinoma

NEERA GUPTA, A K SRIVASTAVA

SUMMARY

Renal cell carcinoma accounts for approximately 3% of adult malignancies and 90-95% of neoplasms arising from the kidney. It is characterized by a lack of early warning signs, diverse clinical manifestations, resistance to radiation and chemotherapy, and infrequent but reproducible responses to immunotherapeutic agents such as interferon- α and interleukin (IL)-2. Performance status IL-6, CRP, LDH, and ESR have been used as prognostic factors for the disease. Herein we review various combination therapies under trial, immunotherapies and upcoming potential therapies in the management of RCC.

INTRODUCTION

The worldwide incidence of renal cell carcinoma (RCC) is increasing at an annual rate of 2%. Men are affected twice as often as women. RCC is tumour of adults, occurring primarily in fourth and sixth decades of life. The cause of RCC is unknown, the factors associated with increased risk include- smoking (relative risk is 2.3 for heavy smokers), urban living, family history of renal cancer, thorotrast exposure, Von hippel-lindau disease and some unproven factors like polycystic kidney disease, diabetes, and chronic dialysis also contribute to this.¹ Histologically adenocarcinomas (historically named hypernephromas or Grawitz's tumours) make up nearly all renal cancers in adults. Transitional cell carcinomas accounts for about 10% of cases that arise in the renal pelvis and often affect multiple sites of urothelial mucosa,

including the renal pelvis, ureters and urinary bladder¹

TNM staging of renal cell carcinoma (adapted from ref. 1)

Tumour (T)

Tx	Primary tumour cannot be assessed
To	No evidence of primary tumour
T1	Tumour \leq 7cm in greatest dimension, limited to the kidneys
T1a	Tumour \leq 4cm in greatest dimension, limited to the kidneys
T1b	Tumour > 4cm but not > 7 cm in greatest dimension, limited to kidneys
T2	Tumour > 7cm in greatest dimension, limited to the kidneys
T3	Tumour extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
T3a	Tumour directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumour grossly into renal vein or its segmental (muscle-containing) branches, or vena cava below diaphragm
T3c	Tumour grossly extends into vena cava above diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota's fascia

Lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
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- No No regional lymph node metastasis
- N1 Metastasis in a single regional lymph node
- N2 Metastasis in more than one regional lymph node

Distant metastasis (M)

- Mx Distant metastasis cannot be assessed
- Mo No distant metastasis
- M1 Distant metastasis

Stage Groupings

Stage I	T 1	N0	M0
Stage II	T 2	N0	M0
Stage III	T 1	N1	M0
	T 2	N1	M0
	T 3a	N0-N1	M0
	T 3b	N0-N1	M0
	T 3c	N0-N1	M0
Stage IV	T 4	N0-N1	M0
	Any T	N2	M0
	Any T	Any N	M1

Management:

Early Disease(Stage I & II)

Radical nephrectomy is the treatment of choice and is the only curative modality of treatment in early stage. Chemotherapy and radiotherapy have no established role in the management of early stage disease.¹

Advanced Disease- (Stage III & IV)

In advanced disease, the intention of treatment is palliation. Less than 1% of patient have chance of spontaneous regression of metastases after nephrectomy. Palliative nephrectomy is indicated in patients with metastases to (i) alleviate severe symptoms such as pain (ii) paraneoplastic syndrome (iii) severe hemorrhage if performance status of the patient is at least 30% on Karnofsky’s scale. It is also

done for patients with good performance status before biological therapy.

Resection of metastasis can be considered if the following criteria are met:

- (1) The interval from nephrectomy to the detection of metastases is at least 2 years.
- (2) The metastases is proved to be solitary by all of the following studies: physical examination, normal liver function tests (LFT’s) (normal CAT scan if LFT’s are abnormal), bone scan, chest CAT scan, CAT scan of the brain if the patient has neurologic symptoms.²

Radiotherapy

Radiotherapy is used to control bleeding and pain from the primary tumour particularly in patients whose clinical condition precludes surgery either because of extensive disease or poor general condition. This is also used to palliate symptoms from metastasis to the CNS and bone.

Role of post operative radiation therapy is controversial. However, it may be considered in patients with perinephric fat extension, adrenal invasion or involved margins. A dose of 4500 cGys is used.

Systemic Therapy

Chemotherapy: RCC is conventionally a chemo-refractory disease. High levels of multidrug resistance gene, MDR1 expressed by RCC cells, mediate the resistance to chemotherapy.³ Overall response rate to chemotherapy is < 10%.

Immuno-therapy. The goal of immunotherapy is to boost the body’s immune system to more effectively fight off or destroy cancer cells i.e, adoptive immunotherapy.⁴⁻¹⁰

Interleukin (IL-2) administered in high- dose regimens produces a response rate of 15% to

20% in good risk patients (Table-1) and durable remissions lasting for more than a decade.¹

The various doses schedule⁴ of IL-2 are:

- High dose, intensive short course (2 weeks)
Wk 1- 600,000 to 720,000 U/kg every 8 hourly by short IV infusion, 5 days treatment up to 14 doses followed by 9 days interval.

Wk 2-600,000 to 720,000 U/kg every 8 hourly by short IV infusion, 5 days treatment up to 14 doses.
- Moderate dose, IV bolus or continuous infusion, short course (2 wks)
72,000U/kg every 8 hours for upto 14 doses(5 days), then 9 days rest, then another 5 days(up to 14 doses)
- Subcutaneous injections-daily for 5 days or thrice weekly, prolonged course (6 months)

5 MU/m² daily; 18 MU/m² days 1- 3, 11 MU/m² days 4-5, weekly for 4 weeks, followed by 2 week rest, then repeat.

Combined outpatient sc interferon- α (IFN- α) and SC IL-2, according to the Atzpodien regimen,⁵ achieves long-term survival benefits in a subset of patients with metastatic renal cell carcinoma, both with and without 13-cis-retinoic acid and/or 5-fluorouracil.^{5,6} Other combination regimens with IL-2 are shown in table-2.

Inhalational IL-2 combines good efficacy and improves tolerability. This is especially important for patients with renal cell cancer with pulmonary metastasis, who are not able to benefit from systemic IL-2 therapy. 5-year survival is reported to be 21%.⁷

IL-2 Toxicity:

Significant morbidity and mortality have been associated with high dose IL-2 therapy. Common toxicities include- hypotension, capillary leak syndrome, tachycardia, arrhythmias, oligouria, azotemia, fever, chills,

nausea, vomiting, diarrhoea, itching, erythematous rash, coagulopathy, liver function test abnormalities, thrombocytopenia, leukocytosis, confusion and agitation.

The durable complete responses associated with high-dose bolus IL-2 have not been reported with other schedules, but their overall frequency is low and the toxicity of this approach is substantial.⁸

Interferon - α has been reported to have a response rate of 15 to 20% (particularly for intrathoracic metastases).¹ A multicenter, randomized trial⁹ to determine the effect of each cytokine (IL-2, IFN- α) independently and in combination, showed that response rate with interferon alone was 7.5% (table- 3) and in combination with IL-2 was 18.6 % as shown in table -2.

Nephrectomy followed by IFN therapy results in longer survival in patients with metastatic renal cell cancer than does IFN therapy alone.¹⁰

Progestins used for treatment of patients with metastatic renal cell carcinoma are associated with response rates of less than 15%¹.

Cytotoxic agents The drug reported to produce responses (15 to 20% of patients) include the fluoropyrimidines and vinblastine.¹ Gefitinib, tetrathiomolybdate, irinotecan, FOLFOX-4 (oxaliplatin, fluorouracil, and folinic acid) and IPM(irinotecan, cisplatin, and mitomycin) regimen have also been tried.

Thalidomide is known for its antiangiogenic properties have shown effectiveness in patients with advanced renal cell cancer whose treatment options are limited.¹¹

Combination regimens under trial: Various combination regimens for the treatment of RCC under trial are shown in table-3.

Potential Therapies :

Fourteen single drug therapies employing different mechanism of action were identified for the treat-

Table-1 Interleukin-2 in Metastatic Renal Cell Carcinoma

Treatment Group (ref)	No. Of Patients	Dose/Route/Frequency	Outcome
High dose IL-2 ⁸	255	600,000 to 720,000 IU/Kg 15 min IV infusion every 8 hours over five consecutive days up to 14 consecutive doses	OR: 15 % (37 out of 255), CR-17, PR-20 OS 16.3 months with 10-20% alive at 10 years.
IL-2+IFN+5FU ⁶	132	IL-2 10x10 ⁶ U/m ² SC twice daily days 3 to 5, weeks 1 + 4 and 5 x 10 ⁶ U/m ² , days 1, 3, and 5, weeks 2 + 3: IFN-a 2a 5 x 10 ⁶ U/m ² SC day 1, weeks 1 + 4 and days 1, 3 and 5, weeks 2 + 3: 10 x 10 ⁶ U/m ² days 1,3, and 5, weeks 5 to 8: and IV-FU 1,000 mg/m ² day 1, weeks 5 to 8.	OR 31% CR 5% PR 26% 27% showed disease stabilization
IFN-a+IL-2 ⁹	140	IL-2 five-day continuous IV infusion at a dose of 18x10 ⁶ IU/m ² /day. Two induction cycles and four maintenance cycles, with a 3-week rest period between cycles. Each induction cycle consisted of two five-day courses of IL-2 infusion separated by a six-day break. Each maintenance cycle consisted of a five-day infusion followed by three weeks of no therapy. IFN a-2a at a dose of 6x10 ⁶ IU per day three times a week SC was given during the two IL-2 induction cycles and during each IL-2 maintenance cycle.	RR-18.6% EFS at one year 20%
IFN-a ⁹	147	18x10 ⁶ IU/ day, 3times/wk x 10 weeks as induction treatment and for 13 additional weeks as maintenance treatment.	RR 7.5 % 1 year EFS-12 %

OR: objective response rate, OS: overall survival, CR: complete response, PR: partial response CR: complete response, PR: partial response, RR: response rate. IFN-interferon

Table-2 Combination regimens for the treatment of metastatic Renal cell carcinoma

Treatment Group (Phase)/No. of Patients	Dose/route/ Frequency/	Outcome
Low dose IL-2 +thalidomide with radiotherapy (Phase II) ¹² N=22	Continuous low dose IL-2 (1 mIU/m ² SC) Thalidomide (200 mg/day)	Effective at 60% of the relatively large evaluable sites (soft tissue lesions and bone metastasis)
IFN-a+capecitabine+thalidomide Pilot study ¹³ N=27	Daily SC IFN- a 1 mIU, oral capecitabine 1900 mg/m ² , thalidomide 200-400 mg/day	PR 20%, MR 4%. Stable disease 24% ³ 6 months
IFN-a 2a IFN-a 2a+13-cis-retinoic acid (CRA) Randomized Phase II/III ¹⁴ N=320	IFN daily SC 3-9 MU IFN daily SC 3-9 MU 13-CRA 1 mg/kg/day	Median time to progression 5.1 months in combination vs 3.4 months for IFN alone. Median OS 17.3 months for combination vs 13.2 months for IFN alone.
IFN alfa+thalidomide Phase II ¹⁹ N=37	IFN 5 mU SC t.i.w, thalidomide 100 mg/day escalated to 1000 mg/day	Out of 12 evaluable patients 7 showed stable disease.
Gemcitabine +5 FU Phase II ¹⁶ N=39	IV gemcitabine 600 mg/m ² over 30 minutes on days 1, 8, and 15 and 5 FU 150 mg/m ² /day continuous IV infusion days 1 to 21 of a 28 day cycle.	OR 17% 7 patients PR 5 patients MR Median progression free survival 28.7 weeks

OR : objective response, MR: minor response, PR: partial response, IFN-a interferon alpha, 13-CRA=cis retinoid acid, mIU-million i.u. OR-objective response

Table-3 Investigative therapies for treatment of metastatic Renal Cell Carcinoma

Treatment Group Mechanism Of Action (Phase)/No. Of Patients/	Dose/Route/ Frequency	Outcome
Bortezomib (29S proteasome inhibitor) Phase II ¹⁷ N= 37	3- 1.5 mg/m ² IV twice weekly for two weeks followed by one week without treatment. Until disease progression or unacceptable toxicity.	PR-4/37 Stable disease
Troxacitabine (BCH4556) Phase II ¹⁸ N= 33 (Nucleoside analogue causes chain termination)	10 mg/m ² IV infusion over 30 minutes once every 3 weeks	PR-2/33 Stable-21/33 median duration of response : 4.4 months
Bevacizumab (Antiangiogenic agent, VEGFR inhibitor) Randomized Phase II ¹⁸ N= 116	Low dose 3 mg/kg, Vs high dose 10 mg/kg IV every two weeks	High dose group- or 10% time to prgression compared to low dose group (4.8 Vs 2.5 months)
Bevacizumab+ Erlotinib ² (Tyrosine kinase Inhibitor) N=58	Bevacizumab 10 mg/kg IV Erlotinib 150 mg/day oral	CR 3% PR 22% Minor/Stable response 44%/40% Median survival-23 months
Sunitinib ² (Tyrosine Kinase Inhibitor), Phase II N=106	Orally at 50 mg daily for 4 weeks followed by a 2-week rest period	PR 29% (1 patient with CR and 16 with PR) 83 assessable pts have ³ 30% decrease in tumour size
Sorafenib ² (Multi-Kinase Inhibitor) Randomized Phase III N=884	Sorafenib 400 mg bid oral Vs Placebo	TTP with soraenib 24 weeks Vs 12 weeks with placebo. PR 2% MR or SD 78%

TTP : time to tumour progression, CR: Complete response, PR: partial response, OR - ojective response rate

RR: response rate, TTP: time to tumour prgression, PR: partial response, MR: minor reponse, SD: stable disease

ment of renal cell cancer. Six distinct area of clinical research have emerged: monoclonal antibodies, small molecules, vaccines, second-generation taxanes, nanopeptides and immunomodulators. Some of the potential therapies under trial are shown in table-3.

Monoclonal antibodies: Four high affinity monoclonal antibodies have recently been tested in the renal cell cancer viz. cetuximab, ABX-EGF, bevacizumab and G250. Cetuximab and ABX-EGF target EGF receptors that are over expressed as high as 91 % in renal cell cancer.¹⁹⁻²⁰

Bevacizumab targets VEGF, a key regulator of angiogenesis. Therapeutic targeting of VEGF in renal cancer has strong biologic rationale and preliminary clinical efficacy.¹⁹

Sorafenib- A multikinase inhibitor, sorafenib has recently been approved for the treatment of metastatic renal cell carcinoma.² It targets the tumour cell (serine/threonine RAF, receptor tyrosine kinase KIT, FLT-3, RET), and tumour vasculature (receptor tyrosine kinases VEGFR-2, VEGFR-3, PDGFR-B). In a placebo controlled, randomized phase III trial in 884 patients, sorafenib was used as second line therapy for metastatic RCC. Sorafenib significantly improves progression free survival compared with placebo (table-3).

Antineoplastic effects of partially HLA-Matched irradiated blood mononuclear cells: Irradiated allogeneic blood mononuclear cells administered outside the context of hemopoietic stem-cell transplantation may induce disease responses in patients with relapsed or refractory renal cell carcinoma.²¹

Table-4 Stem cell transplantation in renal cell carcinoma

Reference	Author (Year)	No of Patients	Conditioning Regimen	Outcome
24	Child et al (2000)	19	Fludarabine + cyclophosphamide	RR 10/19(53%) CR-3, PR-7 9/19 patients alive at 287-831 days after transplant
25	Brain et al (2002)	15	Fludarabine + Cyclophosphamide+ Mycophenolate mofetil	PR-33% 44% had sustained donor engraftment
26	Artz et al (2005)	18	Fludarabine + cyclophosphamide	OR 4/18, all partial Median duration of response-609 days (range 107-926 days) Median overall survival for cohort- 14 months
27	Roigas et al (2005)	100 World literature review	Fludarabine + cyclophosphamide	OR 23%

OR–Overall response, CR–Complete response, PR-Partial response

Adjuvant autologous renal tumour cell vaccine in patients with renal cell carcinoma after radical nephrectomy: Phase III, Randomized controlled trial-Adjuvant treatment with autologous renal tumour cell vaccine in patients with renal cell carcinoma after radical nephrectomy seems to be beneficial and can be considered in patients undergoing radical nephrectomy due to organ confined renal cell carcinoma of more than 2.5 cm in diameter.²²

In a phase II study efficacy of HSPPC-96 (heat shock protein peptide complex vaccine) has also been tested.²³

Stem cell transplant-Allogeneic non-myeloablative hematopoietic stem cell transplantation (NST) and donor lymphocyte infusions (DLI) a form of immunotherapy are currently under clinical investigation as an innovative therapeutic option for patients with metastatic RCC. It has mostly been used after failure of IL2 or interferon. It is possible to replace the patient's immune system with less drastic conditioning chemotherapy than with myeloablative transplants. NST leads to durable responses in a minority of metastatic RCC patients with prolonged survival in responders.²⁴ Some of the studies with NST are shown in table-7.

CONCLUSION:

The course of renal cell cancer is extremely variable, ranging from spontaneous remission to disease progression refractory to chemotherapy. Immunotherapy has held promise of improving clinical outcome. However, despite the wealth of new clinical data on numerous innovative single or combination therapies, responses are still modest and none exhibit significant activity than historical control. Despite advances in our fundamental knowledge of renal cancer biology and newer therapeutics, it becomes essential that all patients need to be taken on a clinical trial or offered best supportive care.

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