
Management of Metastatic Renal Cell Carcinoma

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SUMMARY :

Renal cell carcinoma is the most lethal malignancy of all the urologic malignancies. Outcome of those with metastatic disease is dismal with less than 50% surviving beyond 1 year. Several therapeutic strategies have been tried to improve the survival of these patients. Conventional chemotherapy regimens, single or in combination failed to improve the response rates. Demonstration of immunogenicity in metastatic renal cell carcinoma gave birth to the concept of immunomodulation as potential treatment strategy in this setting. Though the response rates were better than chemotherapy but occurrence of higher adverse effects limits their use. Exploiting the immune response against tumour with the help of non myeloablative transplant, monoclonal antibody therapy and tumour vaccines have shown promising results in phase I / II trials. Newer chemotherapeutic agents like gemcitabine, capecitabine and novel agents like retinoids are being used in phase II trials. Radiotherapy does not have much role to play in metastatic setting except for palliation of painful bone lesions. This review focuses on the various treatment options available for metastatic renal cell carcinoma.

INTRODUCTION

Renal cell carcinoma (RCC) is a relatively uncommon malignancy. It constitutes approximately 3% of all adult malignant tumours.¹

There has been a steady rise in the incidence of renal cell carcinoma, at the rate of 2.3%-4.3% annually.² Incidental detection of malignancy because of increasing use of abdominal imaging techniques has also contributed to the rising incidence. Usually the median age of the diagnosis is 65 years. Males are two to three times at higher risk of developing renal cell carcinoma. One third of the patients may have metastatic disease at presentation.³ Patients who were treated with radical nephrectomy for localized disease, reveal the presence of metastases in 50% of cases at relapse.⁴ Prognosis is dismal in patients with metastatic RCC with 5-year survival rates of less than 10% and median survival of less than 1 year.⁵

PROGNOSTIC FACTORS IN METASTATIC RENAL CELL CARCINOMA

Prognostic factors are very important in stratification of the patients in clinical trials so that data from different centers and studies can be compared. Prognostic factors also help in deciding the appropriate management for particular risk group. Different groups have suggested several prognostic factors. These include presence of synchronous metastases, performance status, the metastases free interval, the site and burden of disease, and the presence of significant weight loss, anemia and hypercalcemia.⁶

In a study of 181 patients with metastatic renal cell carcinoma, lung only metastatic site, good performance status and a metastases free interval of 24 months or more were found to correlate with better survival.⁷ Relationship

between pretherapy clinical laboratory parameters and survival was examined by Motzer and colleagues in advanced RCC.⁸ On the basis of multivariate analysis five factors correlated with poor outcome. These included KPS <80%, high serum LDH levels (>1.5 times normal), anemia, hypercalcemia (corrected calcium >10 mg/dL) and no history of prior nephrectomy. Based on these factors, patients were stratified into three risk groups- low risk (no risk factors), intermediate risk (one or two risk factors), high risk group (>3 risk factors). Median survival was 20 months, 10 months and 4 months for low, intermediate and high-risk groups respectively.

Kavolius and colleagues⁹ documented the role of metastatectomy in improving the survival in metastatic renal cell carcinoma, by reducing the total volume of disease. They also showed that only lung metastasis was associated with better prognosis while brain metastasis or occurrence of multiple metastases corroborates with poor outcome. Metastases to bone and liver fall in between these two extremes.

In addition to these prognostic factors and predictive algorithms for overall survival and disease specific survival, a model has been formulated for patients with metastatic RCC who were treated with combination of cytoreduction and immunotherapy with IL-2, to predict the survival. A scoring system was developed based on the features which were found to be significant on multivariate analysis. These include lymph node status, constitutional symptoms, location of metastases (lung, bone, multiple metastases, other sites), sarcomatoid histology and TSH levels in serum. Based on this, patients were stratified into low (score = 0), intermediate (score = 1 to 5), high (score >5) risk groups. Estimated survival rates at 1 year, 3 years and 5 years were 92%, 61%, 41% for low risk group, and 66%, 31%, 19%, respectively, for the intermediate risk group. The high risk group had 1% survival at 1 year and no survivor at 3 years.¹⁰ Although there are no well established prognostic factors in metastatic renal cell carcinoma but site of metastases, number of metastatic sites, performance status, presence of symptoms seem to be important in determining the outcome.

TREATMENT OPTIONS IN METASTATIC RENAL CELL CARCINOMA

Metastatic renal cell carcinoma (MRCC) is a heterogeneous disease with variable growth rates and periods of stable disease. Looking at the wide range of therapeutic strategies available for MRCC it is evident that none of them have proven beneficial beyond a particular extent. The various options which are available for treating MRCC include 1) cytoreductive nephrectomy 2) chemotherapy 3) Immuno-therapy- Cytokines, adoptive immunotherapy, immunomodulators, allogeneic stem cell transplant, monoclonal antibody therapy, tumour vaccines and 4) Novel therapies like retinoids, tyrosine kinase inhibitors, proteasome inhibitors.

1) CYTOREDUCTIVE NEPHRECTOMY

The concept of cytoreduction in metastatic setting seems logical because of two reasons (i) observation of spontaneous regression of metastatic disease after nephrectomy (ii) Primary tumour is usually unresponsive to systemic therapy.

Incidence of regression of metastatic disease is variable (1%-4.4%).¹¹ It has been observed that the metastatic disease in lungs, which regresses after nephrectomy is probably related with unique biology of primary lesion and pulmonary metastases. In addition to the above-mentioned reasons, the proponents of cytoreduction propose that it leads to palliation of local symptoms and improvement of paraneoplastic phenomenon thereby improving the quality of life. Cytoreductive nephrectomy may also improve the response to chemotherapy. The disadvantages of cytoreduction are perioperative mortality, morbidity and delay in institution of systemic therapy. Patients may progress in perioperative period leading to inferior response to systemic therapy. There are several retrospective single institution series on the role of cytoreductive nephrectomy (Table-1). The rate of perioperative mortality varies widely from 0-17%, so also the number of patients who could not receive systemic therapy (2-77%).¹²⁻¹⁸ Subsequently two-phase III randomized trials have been conducted to exactly define the role of

surgery in MRCC. In EORTC study,¹⁵ 85 patients with MRCC were randomized into two arms (nephrectomy + IFN- α or IFN α alone). There was no significant difference in response rates (17% versus 12%) but the overall survival was significantly better in nephrectomy arm

(12.5 months versus 8.1 months). Similar results were reproduced by SWOG study,¹³ (241 patients), but the responses were remarkably lower than EORTC study (3.3 and 3.6 % in combination and interferon alone arm respectively).

Table-1: Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma : Results.

Study	Patients (No)	Mortality (%)	Response Rate (%)
Rackley et al, 1994 (12)	37	2.7	8.1
Wood et al,2001 (16)	126	1.6	Not reported
Franklin et al,1996 (14)	63	0	33.9
Walther et al,1997 (18)	195	1.0	17.8
SWOG trial, 2001 (13)	120	0.8	3.3
EORTC trial,2001 (15)	42	0	19.0

It has been suggested that overall responses can be improved by combining more effective systemic therapy such as IL-2 with nephrectomy. This combination has been shown to be effective in MRCC in a trial conducted by UCLA group.¹⁹

Hence cytoreduction has a role to play in MRCC provided the patient selection is careful. Patients with poor performance status (ECOG > 1), significant co- morbidities, high volume metastatic disease, brain, liver or bone

metastases, tumour showing sarcomatoid histology should not be considered for surgery.

2) CHEMOTHERAPY IN METASTATIC RENAL CELL CARCINOMA (TABLE-2)

Classical RCC is resistant to many treatment modalities making this malignancy extremely difficult to treat. Yagoda et al have analyzed the results of chemotherapeutic drugs in metastatic RCC and concluded that it is a chemotherapeutically resistant cancer in view of poor overall response rates (<10%).²⁰

Table-2: Results of chemotherapeutic agents in Metastatic Renal Cell Carcinoma

Chemotherapy	Patients (No.)	Objective response rates (%)
Vinblastine (22)	26	4
Floxuridine (25)	82	10
Capectabine (26)	26	30
Gemcitabine+5-Flourouracil (27)	41	17
FOLFOX (28)	59	4

SINGLE AGENT CHEMOTHERAPY REGIMENS

None of the single agent chemotherapy protocols result in response rates of greater than 4-6%²¹. Initial trials were mainly with two agents vinblastine and 5-FU/5-fluorodeoxyuridine. Both these agents showed promising results in MRCC in these early trials. But subsequent trials failed to reproduce these results. In an EORTC trial²², vinblastine as a single agent produced only 4% response rates. Similarly, a randomized trial comparing vinblastine with vinblastine + IFN- α showed only 2.5% response rate in vinblastine alone arm.²³

Role of 5FU/5FUdR has been evaluated in metastatic renal cell carcinoma, using continuous intravenous infusion and circadian modified infusion schedules in various trials. Results were poor and do not favour its use in MRCC as single agent^{24,25}. Capecitabine has been evaluated in a group of 26 patients who failed cytokine therapy. This drug showed activity (Partial response-8.7%, minor response-21.7%, stable disease-56.5%) and favourable toxicity profile in this group of patients²⁶. Taking lead from this trial, combination of capecitabine with other agents is being evaluated. Several newer agents like Troxacitabine, Onconase, Irofulven also failed to show any response. In a phase II trial by Thodtman et al²⁷, multitargeted antifolate, pemetrexed was evaluated in 39 patients of MRCC (untreated). This showed moderate activity (Partial response-3 patients, stable disease- 22 patients, time to progression-5.7 months). This drug needs to be studied in combination with other active agents.

COMBINATION CHEMOTHERAPY REGIMENS:

After failure of single agent chemotherapy several different combinations have been investigated in MRCC. Droz et al²⁸ compiled the data from 153 patients of MRCC treated at single institution with 5 different chemotherapy protocols. Results were extremely disappointing (<10% objective responses). With the advent of newer drugs, combination of gemcitabine and 5FU has been evaluated in a phase II study. This combination was well tolerated with overall response rates of 30%²⁹. Oxaliplatin, a newer platinum analogue, however has been disappointing as part of a combination regimen (FOLFOX).³⁰

Chemotherapy has a role to play in sarcomatoid variant of renal cell carcinoma and

collecting duct carcinoma. Durable responses have been documented with gemcitabine and doxorubicin and MAID regimen (mesna, adriamycin, ifosfamide and dacarbazine).^{31,32}

Such chemoresistance has been attributed to the presence of MDR-ATP dependent efflux pump. So to improve the efficacy, combination of MDR inhibitors (verapamil, cyclosporine) and chemotherapeutic agents have also been investigated but with out any improvement in responses.³³

RETINOIDS

With phase II trials in epithelial cancers documenting the improvement in major responses with combination of IFN- α and retinoids,³⁴ this combination has become an area of potential research in renal cell carcinoma.

In vitro studies had shown that RCC cells are deficient in retinoids³⁵. Therefore it was proposed that with supplementation of the retinoids there would be an improvement in retinoic acid pathway signalling and improvement in the IFN- α responses and the duration of response.³⁶

Both 13-Cis- Retinoic acid (CRA) and ATRA have been investigated. In a phase II trial combination of 13-CRA and IFN- α showed 30% overall response. It needs to be emphasized that responses were seen both at primary and metastatic sites (not a case with any form of chemotherapy or immunotherapy).³⁷

There are two phase III trials evaluating 13-CRA in combination with immunotherapy (IFN- α) or chemoimmunotherapy (5FU+IL-2+IFN- α). Both trials have shown better responses and improvement in median survival in combination arm (containing 13-CRA).^{38,39}

ATRA is biologically more active retinoid but pharmacokinetics of oral ATRA is such that its bioavailability becomes poor after few days of oral administration. So the intravenous and liposomal preparation are being investigated in various phase II trials.⁴⁰ Bexarotene a retinoid - X- receptor selective agonist also showed improvement in response rates as compared with historical controls, when combined with IFN- α .⁴¹

3) IMMUNOTHERAPY IN RENAL CELL CARCINOMA (TABLE-3)

Renal cell carcinoma is considered as an intrinsically immunogenic tumour. The

occasional documented regression of metastases is probably immune mediated. In addition, there are tumour specific antibodies and cytolytic T cells in these patients. Microscopic examination also reveals large infiltrates of T-cells and macrophages in tumour specimen. Considering these facts it was thought that boosting the immune response may be helpful in treatment of this chemoresistant malignancy.

INTERFERON

Interferons are the cytokines, which can regulate the tumour immunogenicity by (i) stimulating cytolytic T lymphocytes (ii) up regulation of MHC expression on tumour cells (iii) regulation of natural killer cells and macrophages. They promote cellular differentiation. In addition, they have antiangiogenic and antiproliferative action.

In MRCC, IFN α -2b has shown responses, varying from 8-29%. Majority of them are partial responses. Time required for response can vary from 2-12 months. Therefore only intermediate doses can be used for such long time to avoid undue toxicities. Doses usually vary from 5-20 MIU/day, 3-5 days per week. Usually the responses are short lived.^{42,43} Other forms like IFN- β and IFN- γ are not active in this malignancy.^{44,45}

INTERLEUKIN -2 (IL-2)

The only US-FDA approved agent for MRCC is IL-2. A trial was conducted in 255 patients of advanced RCC with IL-2-720,000 IU/kg as IV bolus infusion⁴⁶. A total of 14 doses were administered over 5 days. The overall response rate was 15% with median

duration of response being 54 months. However, this dose was found to be highly toxic with side effects like capillary leak syndrome, azotemia, hypotension, liver dysfunction, arrhythmia, congestive heart failure, requiring intensive care set up for administration. Therefore, several other modes of administration (subcutaneous, inhalational, continuous intravenous infusion) and lower dose schedules have been investigated. Lower dose schedules (60-72,000 IU/kg) produce less toxicity. An NCI trial is on going comparing IV high dose IL-2, IV low dose IL-2 and subcutaneous IL-2. Interim results seem to favour high dose IL-2 than other two modes.⁴⁷

COMBINATION OF IL-2 AND IFN - α

The rationale behind this combination was that if interferon alpha could augment the immunogenicity of tumour cells rendering them more susceptible to IL-2 stimulated lymphocytes then this combination may improve the efficacy of IL-2 and lower the dose of IL-2 to decrease the toxicity.

Two-phase III trials in metastatic RCC have compared IL-2 monotherapy with combination cytokine therapy. In first trial, 425 patients were randomized in three arms: continuous IV infusion of IL-2 alone, IFN- α alone and combination of IL-2 + IFN- α . The response rates (6.5% versus 7.5% versus 18.6%) and the 1-year event free survival rate favoured the combination arm. However the overall survival was almost similar in all three groups.⁴⁸ Another trial comparing high dose bolus IL-2 with low dose IL-2 + IFN- α showed a trend towards improved response rate in high dose arm.⁴⁹

Table-3: Results of phase II and III trials with Interferon and IL-2 in metastatic renal cell carcinoma

Immunotherapy	Patients (No)	Response rates (%)
IL-2 - High dose 600,000 or 720,000 (46)	255	15
IFN- α 2a (43)	15	10
IL-2 (CIV)	138	6.5
IFN- α	147	7.5
IL-2 + IFN- α (50)	140	18.6
IL-2 (High dose bolus)	94	25
IL-2+IFN- α (49)	99	12

Thus more mature data and phase III trials are needed to document the superiority of combination over single agent or vice-versa.

ADOPTIVE IMMUNOTHERAPY

Adoptive Immunotherapy refers to the passive transfer of immune cells with antitumour activity into the host. Lymphokine activated killer cells and tumour infiltrating lymphocytes have been studied. In this regard IL-2 is administered concomitantly. None of the trials showed superior response rate with these modalities.^{51,52} Other interleukins have also been investigated but only IL-12 shows some promising results. More trials are needed to clearly define its role.⁵³

COMBINED CHEMO-IMMUNOTHERAPY

Because of poor response rates, various probable combinations have been tried in MRCC. Combination of chemotherapy with immunotherapy was one of such attempt.

In view of earlier trials documenting some role of vinblastine and 5FU, these drugs were combined with cytokine therapy. In a phase III trial of Vinblastine +/-IFN- α in 160 patients, there was statistically significant difference in overall response rates (2.5% versus 16.5% respectively) and median survival (37.8 weeks versus 67.6 weeks respectively) between the two arms favouring the combination arm.²³

Trials with 5FU and IFN- α combination were disappointing. Currently the ongoing preliminary trials are evaluating the combination of cytokines with gemcitabine or capecitabine.^{54,55}

Triple therapy i.e. 5FU+IFN+IL-2 has been shown to be of benefit by few initial trials but subsequent trials failed to reproduce those results.⁵⁶ A phase III trial has evaluated combined cytokine therapy (IL-2+IFN- α) with or without 5-FU in 131 patients with no difference in response rates or progression free survival concluding that there does not seem to be any role of including 5FU in combined cytokine therapy,⁵⁷ but there are trials suggesting that it may produce disease stabilization in patients who fail combined cytokine therapy.⁵⁸

ALLOGENEIC STEM CELL TRANSPLANT IN METASTATIC RENAL CELL CANCER

There are evidences to suggest that RCC is an immunogenic malignancy. But considering the poor response rates of immunotherapy it becomes evident that it has mechanisms to evade the antitumour response. The possible mechanisms of immune dysfunction are both the host and tumour related. They include defects in receptors, signal transduction & induction of apoptosis and tolerance in cytolytic T cells infiltrating the tumour. This concept of immune dysfunction gave birth to the idea of immune replacement for the treatment of MRCC.

Since the myeloablative transplants are associated with high mortality therefore the role of non-myeloablative transplant was investigated in MRCC. It aims to provide enough immunosuppression to allow engraftment of HLA matched donor immune system. Post transplant, allogeneic immune system i.e. the nontolerized T cells overcome the tumour tolerance. These cells recognize tumour specific antigens and minor histocompatibility antigen. Depending on the extent of expression of these minor histocompatibility antigen (tumour restricted or extensive) chances of GVHD vary.

In allogeneic transplant for MRCC there is a need for rapid immune engraftment to avoid rapid tumour growth and tolerance induction. The ideal candidate of allogeneic SCT is the one who has i) failed cytokine therapy (ii) progressive metastatic disease (iii) expected survival >6 months (iv) no CNS involvement (v) no hypercalcemia (vi) HLA matched sibling. The reported trials^{58,59,60} with allogeneic SCT have had very limited number of patients. Different conditioning regimens have been used (cyclophosphamide, fludarabine, ATG thiotepa, busulfan in different combinations); cyclosporine and methotrexate were used for GVHD prophylaxis (except for Tacrolimus & MMF in one study). Bregni et al⁶¹ treated 7 patients of MRCC with allogeneic nonmyeloablative stem cell transplant. Four of the seven patients had partial regression. The incidence of GVHD was low and engraftment occurred in most patients. Child's et al⁵⁹

published the preliminary results of their phase II trial. Ten of the first 19 patients treated had radiographic evidence of disease regression (complete response-3 and partial response-7). Most of the trials show that there is regression or stabilization of disease post transplant. However there is a need for larger trials to make any definite conclusions about its role. Currently transplant may be considered in a young patient with MRCC who has HLA matched sibling and good performance status as a part of clinical trial.

MONOCLONAL ANTIBODY THERAPY

Monoclonal antibody against G250 has been evaluated in MRCC patients. It fulfills all the criteria required for any effective monoclonal antibody i.e.

1. It has very high expression in RCC cells.
2. It is very specific in its expression, only other cells which react with this antibody are gastric mucosal cells and cells of large biliary channels.
3. It is expressed homogeneously.
4. It has an extra ordinary high uptake, so requirement of protein dose is low for tumour saturation.

Initially murine form was used. The overall survival seemed to be better than historical controls.⁶² Myelosuppression, liver dysfunction and the development of HAMA were some of the major problems encountered with the murine form. To overcome this, chimeric version was developed. Currently there are trials evaluating the combination of cytokines with monoclonal antibody therapy. Results are awaited but this targeted approach seems to be promising in early studies.

TUMOUR VACCINES

Boosting the immune response against tumour cells may help in MRCC. Initially gene modified tumour vaccines (GMTV) were generated by transducing IL's/ GM - CSF genes into tumour cells.^{63,64} Trial using the GMTV showed some response without any dose limiting toxicity. But use of GMTV's was limited because of technical

difficulty in generating tumour cell lines. Usually the gene expression is variable in transfected cells. Also there were few safety concerns linked with GMTV's, like spread of genetic material to nonmalignant tissues or germ line and the immunogenicity of viral proteins.

With above concerns, focus was directed towards development of dendritic cell vaccines as dendritic cells are the most important antigens presenting cells. They express both class I antigens & II and can induce cytolytic T cell response as well as the memory T cells.

They can be obtained from peripheral blood mononuclear cells (CD14+ monocytes) or ex vivo from bone marrow precursor cells (CD 34 +). These are then loaded with antigens (peptides proteins, opsonized antigens, tumour lysates, irradiated whole cell preparations, antigens in the form of mRNA) following culture. After maturation they can be injected intradermally, subcutaneously, intravenously or intralymphatic. Among all these routes intralymphatic and intradermal are more effective.

Clinical trials have documented their role in MRCC.^{65,66} They usually produce stable disease or attenuation of growth of tumour, which may not be radiologically evident. There is no evidence of autoimmunity or of dose limiting toxicity. Their role needs to be studied in larger trials especially in terms of survival benefit, as the response is usually only disease stabilization and not regression.

NOVEL THERAPIES

Newer agents like IRESSA have also been studied in MRCC but was not found beneficial.⁶⁷ An animal study suggested role of EGFR inhibitor in combination with taxol for bony metastases as RCC Cells express EGFR receptors benefit.⁶⁸

Renal cell carcinoma is a highly vascular tumour, so antiangiogenic agents like thalidomide have also been tried. There are 9 phase II studies with single agent thalidomide showing a partial response rate of 7% and stable disease in 31% of patients.⁶⁹ Doses are usually escalated from 200 mg to 1200 mg, higher doses

being associated with significant toxicity. The combination of thalidomide and cytokines is also being subjected to phase III trials.

ROLE OF RADIOTHERAPY

This disease is not radiosensitive, so role of radiotherapy is limited. It can be helpful in palliation of patients with painful bony metastases or those who present with neurological deficit.

CONCLUSION

Metastatic renal cell carcinoma is resistant to most of the conventional therapeutic strategies. Combination of different modalities seems to work better than individual modalities. Though the novel therapies are showing promising results in early trials, more mature data is required to develop standard guidelines for the treatment of these patients.

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