Review

The Role of non-surgical options in the treatment of renal cancer:

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Introduction:

Renal cancer accounts for almost 2--3% of all cancers in adults, male female ratio is 3:2, and in 4% of the cases the disease is bilateral. (1, 2). Adencarcinomas form 80 - 90% of all primary renal cancers, which arise from the renal cortex. The second cancer is transitional cell cancer arising from the renal pelvis. Other rare renal cancers include: oncocytomas, sarcomas and medullary cancers. It's more prevalent in the 6 – 8th decades of age, (3, and 4)

Despite improvement in diagnosis, 20 –30% of patients present with metastatic disease and another 20 % of patients undergoing nephrectomy will later develop metastases. The etiology of RCC is unknown but obesity and smoking are risk factors .The highest incidence was reported from Europe, North America and Australia, while rates are low in Africa, India and Japan. In Sudan it forms about 1.5 % of all cancers in adults. (3, 4).

Pathology

The 2004 WHO classification of renal cancers is:

Clear cell cancer (70%); papillary cancers (10 -15%); chromophope tumors (15 %). Other rare renal cancers include: cancer of the collected ducts of Billini; renal medullary cancer; XP12 translocational cancer; multi-locullar clear cell cancer associated with neuroblastoma; mucinous tubular and spindle cell cancer; and unclassified renal cell cancers. Sarcomatoid and rhabdoid differentiation are rare findings that may occur in any subtype with highly aggressive behavior. (5, 6, 7).

Staging

There are many staging systems used, but Robson modification of Flocks and Kadesky is not complicated and is commonly used in clinical practice.

Stage one: tumor confined within the capsule.

Stage two: tumor invading the perinephric fat but still contained within the gertora fascia.

Stage three: tumor invading the renal vein or the inferior vena cava = A, or involving regional nodes = B, or both = C, (8, 9).

Surgery

Surgery remains the main and the most effective treatment for nlocalized disease .It's also used for treatment of metastases and local recurrence as a palliative treatment. Most urologists perform open nephrectomy, with either a retroperitoneal or transperitoneal approach. In the 1960th Robson described the operative principles of radical nephrectomy, which became the gold standard treatment for localized renal cancer. (10, 11).

Radiotherapy

Preoperative radiotherapy and postoperative radiotherapy failed to show any advantage in disease free survival (DFS), or overall survival (OS), based on 2 preoperative and 2 postoperative radiotherapy negative trials. (12, 13)

Radiotherapy can be used in the treatment of unresectable disease, recurrent disease and metastatic disease as a palliative treatment, to improve local control and relieve symptoms. (13)

Prognosis

Despite recent advances in the treatment of renal cell cancer, the prognosis remains poor, with an estimated 5 years survival of 11 %.[1] The disease is resistant to chemotherapy, and a small subset of patients respond to immunotherapy[2,3]. The introduction of the Tyrosine Kinase Inhibitors, Sunitinib , Pazopanib and Axitinib , and the Vascular Endothelial Growth Factor(VEGF); directed Monoclonal Antibody Bevacizumab ,used in combination with interferon and the Mtor inhibitor (Everolimus), and Temsolinimus , increased the progression- free survival (PFS), compared with immunotherapy and placebo. [14]

Many prognostic factors influence treatment decisions and outcome e.g. the pathology is a key factor. Most of the available data are in patients with clear cell renal ca, which accounts for 70 –80 %of the cases. Papillary renal cell cancer, 10 –15%, with a similar prognosis to clear cell RCC; and chromophope renal cell cancer which forms about 5% of the cases has a better prognosis, [15, 16]

Other prognostic factors e.g the Memorial Sloan Kettering model which stratified prognosis as favorable , intermediate or poor based on serum lactic dehydrogenase (LDH), performance status ;serum calcium level >10mg /dl, Hg level less than the lower level of normal; and time from diagnosis to treatment . Score zero has a favorable prognosis ;1-2 factors is intermediate risk; 3 -5 is poor prognosis ,which are associated with: 30,14,5 months median survival respectively. The model was developed for patients treated with interferon-based regimens to identify patients who may benefit from immunotherapy. [17, 18]

Immunotherapy

Alpha interferon daily subcutaneous dose of 5 – 10 million units produces an objective response of 13-15%.The common side effects are flu-like ,fever, chills, anorexia ,muscle ache ,headache and fatigue .The response is usually slow . In a large study of 246 patients randomized to nephrectomy and alpha interferon vs nephrectomy alone ,showed a median survival of 11.1 vs 8.1 months in favor of the alpha interferon group (p = 0.05) and overall survival of 17 vs 7 months in favor of alpha interferon group(p= 003) .[19,20] Alpha interferon and interleukin 2,IL2, were the first approved agents for metastatic RCC, and for two decades this was the standard care. Interferon improves overall survival by 2.5 months compared with hormonal treatment with medroxy progesterone acetate . Its use is limited by adverse effects e.g. influenza like symptoms ,and fatigue ,but these are usually grade 1 or 2.[20]

High dose IL2 produces complete response in 5 – 7% of patients in patients with advanced RCC .It should be considered in patients with excellent cardiopulmonary reserve. Its use is associated with 14% incidence of treatment -related deaths and fever,chills, fatigue ,hypotension , nausea and vomiting [21,22]. Both agents can produce durable responses that can last for years. From the analysis of 7 phase 2 trials, of 255 patients, treated with high dose IL2, complete response was achieved in 7% of patients and partial response in 8 %of patients. Median duration of CR was 80 months and 20 months for PR patients. There is no known factors that can identify patients who will benefit from immunotherapy. [22, 23]

Targeted treatment first line

Sunitinib is an oral multikinase inhibitor. A dose of 50 mg daily for 4 weeks and 2 weeks off in favorable and intermediate risk group patients ,resulted in PFS of 8 – 9 months. There are some safety concerns with regard to fatigue,hand foot syndrome ,diarrhea and hepatic toxicity. So Sunitinib is used as a first line for all prognostic groups patients, particularly those with aggressive disease who are younger and fitter,and less appropriate for elderly patients with co- morbidities. [24]. In a phase 3 study of 750 new patients with clear cell RCC, comparing sunitinib vs alpha interferon ,the median overall survival was 11 vs 5 months in favor of sunitinib. Overall survival showed a statistically non- significant trend in favor of sunitinib : 26.4 vs 21.8 months (p= 0.051).[24,25]

Pazobanib

Is a multikinase inhibitor . It was investigated in a phase 2 study, as first line treatment in 233 patients ,dose 800 mg daily. The median survival was prolonged by 9.2 months vs. 4.2, (p value <0.0001). 53% of these patients developed elevation of transaminases ,in addition to fatigue and anorexia in 19 – 22 % respectively . Currently pazopanib seems to be a reasonable alternative option to sunitinib in patients with good and intermediate prognosis. [26] It was evaluated in a placebo- controlled international study of 435 patients with clear cell RCC ,50%of them had cytokine therapy, and 50% were naïve .The progression- free survival ,PFS, in the pazbanib group was 9.2 vs 4.2 months in the placebo group (p= 0.0001).[27]

Bevacizumab and alpha interferon

Bevacizumab was approved by the FDA in 2009 for the treatment of metastatic RCC .The reported median PFS of bevacizumab and interferron ranges between 8.5 –16.8 months in the AVOREN,CALGB, and the TORAVA Studies .Patients with favorable and or indolent disease may be particularly suitable for bevacizumab and interferon therapy.[28,29,30] Bevacizumab and alpha interferon as a first line treatment resulted in a longer PFS ,but not overall survival compared with alpha interferon alone.[30]

Sorafenib

Many phase 2 studies of first line sorafenib ,showed a median PFS of 5.7 – 9 months. In phase 3 trials sorafenib was associated with lower rates of diarrhea (48 vs. 61), nausea(19vs 52 %) , fatigue(29 vs. 54 %),vomiting (12 vs. 31 %) and hypertension (17 vs. 30%), compared with sunitinib ,but similar rates of hand foot syndrome (33 vs. 29%.[300]

Sequential targeted therapies should be considered in all patients able to tolerate them, particularly those with minimal co- morbidities and younger patients. Several retrospective studies have shown benefit of a sequence of sorafenib and sunitinieb. [31, 32]

Temsirolimus

Is an intravenously given mTOR inhibitor . It was approved by the FDA in May 2007,and in the *NCCN kidney cancer panel recommendations as a category A* for first line treatment for patients with poor prognosis ,relapsed or unresectable or metastatic RCC. In a study of 626 patients randomized for temsirolimus 25 mg/week, vs. alfa interferon alone vs. temsirolimus 15mg and alfa interferon, patients treated with temsirolimus had a longer overall survival (OS), than those treated with alfa interferon alone, (10.9 vs. 7.3 months) median survival (p value = 0.003). Adverse events include: rash, stomatitis, pain, infection, peripheral oedema, thrombocytopenia, neuropathy, hyperlipedemia, hypercholestremia and hyperglycemia.[33, 34, 35]

Everolimus

This is an oral m Tor inhibitor. It was approved by the FDA in 2009, as a second line treatment after sorafenib or sunitinib failure. In a phase 3 study in patients failing sunitinib and or sorafenib in 410 patients, randomized into everolimus 10mg daily(272 patients) vs. placebo (138 patients), everolimus produced significantly better PFS, 4 months vs. 1.9 (p value = 0.0001). Its side effects included: stomatitis 40%, rash 25 %, fatigue 20%, non- infectious pneumonitis 3 %.[36]

A large randomized phase 2 study (RECORD Study), showed that the standard sequence of multiagent tyrosine kinase inhibitors: sunitinib followed by everolimus, extended survival compared with the reverse. [37]

Chemotherapy

RCC is refractory to most chemotherapy agents, because of multi-resistance mediated by p glycoprotein. A phase 2 trials of gemcitabine 600 mg /m^2, day 1, 8 and 15, and 5 FU, 150 mg/m^2 continuous daily infusion for 21 days, in patients with metastatic RCC, produced a partial response in about 17% of patients without any complete response.[38]

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