TARGET THERAPY FOR METASTATIC RENAL CELL CARCINOMA CASE PRESENTATION

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Abstract: *It is a case study of female patient aged 69 years known with no significant family history of malignancies, diagnosed on July 2012 with a 6 th cervical vertebral body voluminous mass, with adjacent spine compression and soft tissue invasion due to persistent neurological symptoms for a several weeks ago. She underwent a tumor ablation with C6 vertebrectomy reconstruction with the use of titan on September 2012. On October 2012 the histopathology and immunohistochemistry report determined that is was a clear cell renal cell carcinoma. Further investigations continued in the oncology department. The toraco-abdominal CT scan in January 2013 identified a right renal apical and 2 right lung apical micronodules and one on the right base. At the time of presentation in our Department the patient had a bad Performance Status with cachexy, asthenia and a depressive syndrome that made her non-eligible for cytoreductive surgery. The patient underwent palliative radiotherapy on the cervical region: 30y in 10 fractions (over 2 weeks). On January 2013 the patient started first line treatment for mRCC with Bevacizumab and Interferone with partial remission of the target lesion on follow-up CT scan (June 2015). Second line treatment for metastatic cancer consists of on TKI (Sunitinib) and was stopped after almost 22 months of stable disease (April 2016). Our patient started Everolimus (mTOR inhibitor) on Apr 2017 and continues today with a stable disease, good Performane Status and no pain. Conclusions: Multidisciplinary management is needed for mRCC patients suffering from bone metastasis. New agents have become available to treat renal cell cancer (RCC) in recent years, wich increased overall survival with a good Quality of life.*

INTRODUCTION

Worldwide, the incidence of kidney cancer is about 3% - 5% of all malignancies for adult and for the both sexes.(1) More than 50% of kidney cancers are diagnosed incidentally. The three classic clinical signs such as flank pain, macroscopic haematuria and palpable abdominal mass are less frequent identified than in the past.(2) A rate of 30% of patients with kidney carcinoma have metastatic disease at diagnosis and 20% of them have bone metastases.(3) Often bone metastases are present at diagnosis being the first sign of metastatic disease in renal cancer patients. Osteolytic lesions of the axial skeleton with bone resorption rather than new bone formation.(4) A few years ago the treatment for metastatic renal cell carcinoma disease has been palliative; relief of the simptoms especially pain and also prevention of pathological fractures. Today, the new target therapies for metastatic renal cancer has improved overall survival and quality of life for these patients considerably. Cytoreductive nephrectomy is now recommended for the patients with good performance status and large symptomatic kidney tumours and limited metastatic disease and not for patients with alterated performance status.(2) In the first line treatment of metastatic disease for the patients with good performance status and good or intermediate prognosis the treatments with monoclonal antibodies like bevacizumab associated with interferon, sunitinib and pazopanib.(2) Surgery o the spinal metastases ideally should be carried out before irradiation. Irradiation which preceding surgery has a significantly higher complication rate.(5,6,7)

CASE PRESENTATION

It is a case study of a female patient aged 69 years, urban resident, non-smoker and with no exposure to toxic environmental agents. She presented with persistent neck pain, neurological deficit, paraesthesia of the both upper limbs prevalent in the right, progressive deformity of the cervical vertebral column, and general weakness. The patient was presented to the Neurologist with this symptomatology on July 2012. The pain was either caused by increased intraosseous pressure in the vertebral bodies due to cellular invasion of the bone, by compression of neural structures (cervico-brahial plexus), by a secondary instability due to the osteoligamentous destruction of parts of the axial skeleton, or by the infiltration of the dura or other neuroanatomical structures. A radiography of the cervical region releaves a C6 (the 6th cervical body) spine press due to an osteolytic lesion.

The MRI (27 July 2012) offers a good visualization of a soft tumor involvement: voluminous mass at the level of the 6th cervical body, that appears intensely deformed with adjacent spine compression and soft tissue invasion. In T1-weighted images metastatic tumors appear in a hypodense form, whereas in T2-weighted images tumors of the spine was hyperdense as an expression of an increased water content or replacement of the fatty marrow of the bone by tumor cell. Metastases show gadolinium enhancement.

Surgical treatment; The Neurosurgeon opted on 15.09.2012 for tumor ablation with C6 vertebrectomy, approached by anterior surgery, reconstruction with the use of metal (titan) spacers in combination with cement.

The histopathology and immunohistochemistry report determined that is was stage IV clear cell renal cell carcinoma (hystopathological report on 03.10.2012). The immunohistochemical profile using monoclonal antibodies for CD10 showed positive staining for this marker and focal for CK. Almost 3 months after surgery the patient was admitted in our

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Oncology Department for further investigations and management. The toraco-abdominal CT scan in January 2013 identified a right renal apical mass of 4 cm without right lumbar lymphadenopath and without right renal vein invasion on CT, with 2 right lung apical micronodules and one on the right base (figure no. 1). The stage of the disease was stage IV cT1aNoM1

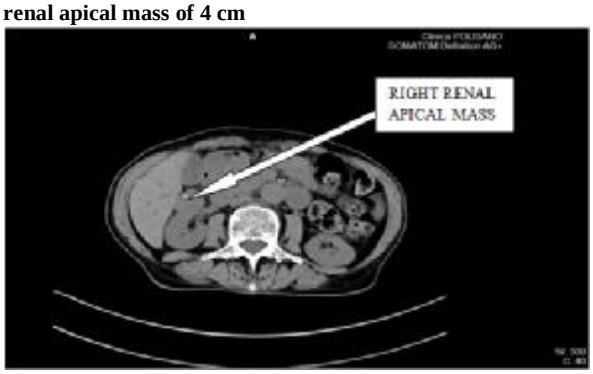
Usually, cytoreduction surgery (nephrectomy) is practiced and recommended for the patients with good performance status and large kidney tumours with limited metastatic disease or symptomatic primary tumor, but not recommended in patients with altered performance status.(2)

At the time of presentation in our Department the patient had a bad PS with cachexy, asthenia and a depressive syndrome that made her non-eligible for cytoreductive surgery.

The patient accepted by informed consent and underwent palliative radiotherapy on the cervical region: 30y in 10 fractions (over 2 weeks).

Taking into consideration the metastatic disease setting and the histology of the tumor a systemic treatment should be initiated, either with a vascular endothelial growth factor (VEGF) inhibitor + Interferon (IFN)-alpha, a tyrosine kinase inhibitors (TKIs) or an (mTOR) inhibitor.

Figure no. 1. Toraco-abdominal CT scan January 2013: renal apical mass of 4 cm



DISCUSSIONS

The gold standard for the risk assessment during target therapyfor metastatic renal cell cancer was implemented by the Memorial Sloane Kettering Cancer Centre (MSKCC).(2,8) The assessment of the MSKCC was introduced with the International Metastatic Renal Cell Cancer Database Consortium (IMDC) score. It was extended the factors to a total number of 6 for a high concordance.(2,9,10) Patient risk factors are presented in table no. 1 and table no. 2.

Table no. 1. Patient risk factors

RISK FACTORS	PATIENT
Karnofsky performance status (PS) <80%	70%
Haemoglobin <lower limit of normal	Haemoglobin
Time from diagnosis to treatment of <1 year	Time from diagnosis to treatment 7 month
Corrected calcium above the upper limit of normal	Calcium=10,5 mg/ml
Platelets greater than the upper limit of normal	Platelets = normal
Neutrophils greater than the upper limit of normal	Neutrophils=normal

Table no. 2. Estimative median overall survival in first- and second-line therapy related to the IMDC risk groups (2)

Number of risk factors	Risk category	First-line median overall survival (months) (11)	Second-line median overall survival (months) (11)
0	Favourable	43.2	16.6
1–2	Intermediate	35.3	7.8
3–6	Unfavourable	22.5	5.4

Selection of the optimal therapy was made after risk assessment using the Memorial Sloan Kettering Cancer Center (MSKCC) updated score, which stratified our patient into the intermediate risk group, seeing that he presented with one out of six.

The target treatments which marked efficacy in phase III trials were bevacizumab with interferon, sunitinib and pazopanib.(2,12,8,13) The inhibition of the vascular endothelial growth factor (anti-VEGF) is a valid therapeutic approach in renal cell carcinoma. The treatment consists from a combination of the humanised anti-VEGF monoclonal antibody bevacizumab with interferon alfa.

Our patient started first line treatment for mRCC on January 2013 with Bevacizumab and Interferone. She recived interferon alfa-2a (9 MIU subcutaneously three times weekly) and bevacizumab (10 mg/kg every 2 weeks).

At 29 months of treatment with bevacizumab and interferone, the renal mass had a partial remission without new lesions. No adverse events have been observed on the first line treatment.

Following 3 months of treatment, CT scan (full scan) showed a partial remission (reduction 50%) of the renal cell mass without new lesions. The patient had a stable disease until June 2015 when the CT scan showed a progression of the renal tumor and 2 new lung lesions (5 mm) in the lower bilateral pulmonary lobes. Bevacizumab and interferon treatment was discontinued and started the second line systemic treatment wth Sunitinib.

After treatment VEGF-targeted therapy in the first line, both axitinib and everolimus are active.(2) At the time of disease progression axitinib and everolimus were not approved by the ANM for settlement in the national oncology program. The accessibility for a second line treatment was Sunitinib.

Sunitinib is a receptor tyrosine kinase multiple inhibitor. Sunitinib inhibits selectively the 1, 2, 3 receptors for the vascular endothelial growth factor receptors; the a and b PDGFR (platelet-derived growth factor receptors), the KIT receptor (stem cell factor receptor), the FLT 3 (FMS-like tyrosine kinase-3 receptor) and finally the RET receptor (the glial cell line derived neurotrophic factor).(14) It is an oral target therapy that block growth signals in the cancer cells and leads to cells death. This therapy stops Sunitinib developing new blood vessels to with reducing cancer cells supply of oxygen and nutrients. The result is shrinking and stopping tumour growing. Because it interferes with blood vessel growth it is an angiogenesis inhibitors.(15)

Sunitinib is given at a dose 50 mg/day for 4 consecutive weeks followed by 2 weeks of pause. Overall, the patient has received sunitinib treatment until Apr 2016. Regular, six-monthly CT scans (thoraco-abdomino-pelvic scan) demonstrate that the lung lesion and renal mass had no progression (stable disease). The patient did not have any pain and. She does not require pain drugs. The systemic treatment with TKI was stopped after almost 22 months. At this point we considered another line of systemic treatment. Comparing the latest imaging with the CT scans that showed the second progression under TKI.

After second-line treatment disease progression, the patient is able to be enrolled into clinical trials if it is possible. It was not possible for our patient to be enrolled into a clinical trial and the rational option was the third line target treatment with everolimus.TSC1/TSC2: the hamartin/tuberin complex, is a protein complex produced by the genes TSC1 and TSC2. In normal cells, the function of the TSC1/TSC2 complex is to inhibit mTOR, an important intracellular signalling molecule. By inhibiting mTOR, the TSC1/TSC2 complex helps control the process of cell growth and proliferation. By inhibiting mTOR,

AFINITOR blocks the effects caused by the loss of the *TSC1/TSC2* genes and reduces cell growth, proliferation, and angiogenesis.(16,17) Our patient started Everolimus on Apr 2017. Everolimus treatment continues today. The dose is 10 mg once daily. The patient undergoes the third line everolimus treatment and has a stable disease on the last CT scan evaluation (October 2017). It has a good Performance Status and no pain.
Regular follow-ups have been done during the all three lines treatment period by clinical exams, monitoring the complete blood count and biological parameters. CT scans of the thorax, abdominal and pelvic regions were performed at an interval of approximately 3 months, and than at 6 months throughout the treatment and the active surveillance periods.

The bone metastases in the middle cervical spine the anterior approach with anterior decompression and anterior column reconstruction is effective and has a low morbidity. Surgical management showed a great improvement in pain reduction, but also in quality of life. Surgery ideally should be carried out before irradiation. We report a case of cervical resecable spine metastatic clear cell renal cancer. Cytoreductive nephrectomy was not eligible due to poor performance status at diagnosis despite a cT1 tumor (4 cm/ <7 cm) and limited volume of metastatic lesions (one lesion at C6). The patient achieved long-term survival with three lines of target therapies. The treatment lines were chosen according to the guidelines (ESMO guidelines) and availability at the time of the change in the list of oncological drugs approved on that date by the ANM. The patient has a 63-month survival with good performance status and a good quality of life, with no pain and ability to take care of himself. Target therapies improved the overall survival for metastatic renal cancer. What will be the next treatment choice after progression? For the two lines of treatment with anti-VEGF therapy and mTOR inhibitor, the alternative therapy with activity on metastatic disease is sorafenib.(2) Other monoclonal antibodies that had been shown activity on metastatic disease, Nivolumab or Cabozantinib can be a choice of treatment. Using another TKI or rechallenge with the same TKI may be the option. Enrolment into clinical trials is the alternative if it is possible.

CONCLUSIONS

Multidisciplinary management is needed for metastatic renal cell cancer patients with bone metastasis.

Due to the extent of bone metastasis its location the treatment must be individualised.

Therapeutic options are discussed regarding staging and risk group for clear cell metastatic renal carcinoma.

New agents have become available to treat renal cell cancer (RCC) in recent years, which increased overall survival with a good Quality of life.

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