Review paper

Antiangiogenic treatment in renal cell carcinoma

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Abstract

Renal cell carcinoma (RCC) is the most lethal of all genitourinary tumors which standard and often curative treatment is based on radical nephrectomy or nephron sparing surgery. Since 2009 the treatment of metastatic and advanced RCC, following the cytoreductive surgery, has targeted antiangiogenic therapy combined with immunotherapy. The objective response rate to anti-angiogenic agents targeting VEGF, PDGF and thyrosine kinase inhibition like bevacizumab, sunitynib, sorafenib and others is almost twice higher than in previously used interferon and /or interleukin 2 immunotherapy. Future possibilities in stabilization of kidney cancer were discussed.

Key words: *renal cell carcinoma, angiogenesis, antiangiogenic therapy, immunotherapy.*

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Clear cell type renal cell carcinoma (RCC CCT) originates from mesenchymal cells of the epithelium lining proximal convoluted tubules in kidneys. It accounts for 3% of all cancers and is identified as the most common type of kidney tumor. The disease is usually diagnosed in the sixth decade of life and morbidity amounts to 4/100 000. RCC is twice more common for men than women. Distal metastases develops 30% of patients and postoperative recurrence almost 40% [1, 2]. In Poland the incidence of kidney cancer has been rising steadily (4000/year) and mortality due to the cancer is more than 200 patients every year [2]. Renal cell carcinoma is also known to be the most lethal of all the genitourinary tumors. The tumor etiology is still not very well understood. Long term dialysis, polycystic disease of kidney, exposure to aromatic hydrocarbons (cadm, asbestos, tobacco), obesity, hypertension are mentioned as factor of renal carcinogenesis [3-5]. Hereditary and sporadic forms of RCCCCT are driven by mutation in a Von Hippel-Lindau (VHL) tumor suppressor gene. Family renal tumor history as a genetic factor also increases the risk of the tumor [6]. The kidney parenchymal tumors are most often diagnosed in the presymptomatic stage at the time of the abdominal ultrasound. The clinical stage of the tumor is identified by computed tomgraphy (CT) scan or magnetic resonance imaging (MRI). The grade of cancer cells differentiation is most often unrecognised until the microscopic examination of the specimen. In the majority of urological departments tumor biopsy is not performed due to low diagnostic sensitivity and the risk of spreading cancer cells [7]. Standard and often curative treatment is based on radical nephrectomy, the initial surgical method which includes removing of the kidney with perirenal fat and enlarged lymph nodes [8]. In the last 15 years the tumorectomy known as Nephron Sparing Surgery (NSS) is carried more frequently, especially in cT1 renal tumors (less than seven cm of diameter) and in case of young patients [9, 10]. Based on the observation from the last decade prognosis after both types of operations (radical nephrectomy vs NSS) was equal. Survival rate of 5-10 years in pT1 RCC is properly 95-80%, but this is lowered considerably where metastases have spread [10]. Surgery via laparoscopic or robotic techniques is becoming increasingly popular. It was proved in previous years that renal tumors are resistant to chemo- and radiotherapy. A metastatic or advanced tumor accounts for about one fourth of RCC patients. Since 2009 the treatment of metastatic and advanced RCC, following the initial cytoreductive nephrectomy, has targeted antiangiogenic therapy combined with immunotherapy [11]. The first line antiangiogenic treatment are mainly sunitynib (Sutent) or bevacizumab (Avastin) and temsirolimus (Torisel) for patients with high risk of progresion. Antiangiogenic treatment is presently a standard therapy of metastatic RCC.

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The response rate of antiangiogenic therapy (about 30%) is higher than in previously used interferon and /or interleukin 2 immunotherapy (about 6%) [11]. Sorafenib (Nexavar) or everolimus are applied in the second line of antiangiogenic therapy [12-14]. Pazopanib (Votrient) and rapamycin have also shown promise in improving the prognosis of advanced RCC [15]. The strategy of employing an antiangiogenic therapy definitely improves effectiveness of the cancer stabilization and occasionally results in partial remission. It is beyond the dispute that RCC is a high microvessel density tumor with high expression of angiogenic cytokines like: VEGF, bFGF, TGFB1, angiogenin. Many experimental studies presented the inhibition of tumor growth by endo- and egzogenic angioinhibitory factors like: thrombospondins 1 and 2, interleukin-12, angiostatin, endostatin, PF–4, interferons, cytostatics, antiestrogens, antibiotics (TNP-470), thalidomide, Vit D analogs, captopril and nonsteroid anti-inflammatory drugs. First clinically available in USA bevacizumab (Avastin, BEV) is a humanized monoclonal antibody targeting VEGF-A and blocking tumor angiogenesis. In 649 patients in a multicenter study AVOREN the objective time to progression was almost two times longer (from 2.5 to 4.8 month) and progression free survival was almost twice as long (from 5.4 to 10.2 month) in the BEV group compared to immunotherapy. The response rate was 2 times higher in BEV group (from 13 to 26%). No unexpected adverse events were observed. Sunitynib (Sutent), an oral medication, is multitarget receptor of thyrosine kinase inhibitor approved by FDA for two cancers: gastrointerstinal stromal tumours and renal cell carcinoma. Thyrosine kinase inhibition reduces effects of aberrative VHL gene which produces proangiogenic VEGF and PDGF. Sunitynib inhibits renal tumor angiogenesis by inhibition of proangiogenic genes activity. In a multicontinental trial Motzer and collegues have proved more than a two-fold elongation of time to progression (from 5 to 11 month). The objective response rate is evidently higher in sunitynib group (31%) versus interferon group (6%). Initial results indicate possibility of overall survival improvement in RCC treated by sunitynib . Costs of treatment are high and adverse events occurs in case of 10-15% of patients like hypertension, cardiopulmonary insufficiency and increased lipase level. The optimal dose is 50 mg/d. Temsirolimus (Torisel) is a blocker of kinase receptors alike sunitynib. Authors demonstrate 2.5 longer overall survival in Torisel group versus interferon group in 600 patients. Another oral antiangiogenic thyrosine kinase and PDGFR and VEGF blocker Sorafenib (Nexavar) is applied from 2005/6. Additionally it also blocks Raf-1 – an enzyme involved in cancer cells proliferation. The TARGET renal global evaluation trial with 903 patients demonstrated that sorafenib treatment (50 mg/day) doubled free survival rate and also the time to recurrence from 2.8 to 5.5 month compared to interferon therapy [16-19]. Those results convince that earlier applicable interferon immunotherapy is less effective and antiangiogenic agents are crucial for the treatment. Nevertheless the complete remission of advanced tumor is almost unattainable. Incomplete proangiogenic receptors blockade or hypoxia may induce other growth factors activity (CXCR4, TGF-α and others). That might be one of the reasons of incomplete inhibition of tumor growth. In the majority of advanced parenchymal renal tumors there is a destruction of central part of the tumor due to hypoxia caused by disparity between tumor growth and tumor vascularity. It is possible that incomplete remission is caused by other active pathways that are independent of VEGF but stimulated by FGF or IL-8. The analysis of different proangiogenic factors in the blood or in the tumor tissue during antiangiogenic therapy could elucidate this problem. The other ways to effective antiangiogenic therapy of RCC is development of research over circulating endothelial progenitors cells which promotes endothelial proliferation of new vessels. Unfortunately there are no clinically useful manners of angiogenesis monitoring. MVD measurements is not useful in clinical practice. There are attempts made to use positron emission tomography – computed tomography (PET-CT) for this target with use stamped fructodezoxyglucose.

In conclusion, one may see a progress in stabilization of advanced kidney cancer by new angiogenic inhibitors. In succession of landmark studies three different antiangiogenic agents sunitynib, sorafenib, temsirolimus demonstrated significantly greater antitumor activity in patients with mRCC than any kind of immunotherapy. Trial effects are promising but clinically middling. Perhaps introduction of antiangiogenic poly-therapy which will block parallel pathways of tumor growth jointed with more active surgical cytoreduction may be a chance to obtain further progress of mRCC treatment [20, 21].

For the future, there is also a question of using the antiangiogenic agents for patients with RCC that where operated using NSS method, for avoiding a possible pro-angiogenic and pro-neoplastic activity of remaining kidney tissue.

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