CASE REPORT

Hypofractionated radiotherapy with concomitant sunitinib – is there a radiosensitizing effect?

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We present a case of a patient with metastatic renal cell cancer (RCC) treated with hypofractionated radiotherapy while being treated with sunitinib. He received a single dose of 8 Gy of external beam radiation to a metastatic mass of several centimeters diameter in the right lateral ribs, followed by a second identical dose. Clinically, the patient achieved a nearly complete disappearance of the mass. We discuss the possible synergy between tyrosine kinase receptor inhibitors (TKRIs) and radiotherapy and the importance of dose fractionation.

Key Words: concomitant, sunitinub, radioresistance, renal cell cancer

Clinical synopsis

A previously healthy 55-year-old patient underwent a right nephrectomy for a mass of the upper pole measuring 10 cm x 7.5 cm x 6.0 cm. A grade I clear cell carcinoma with focal necrosis was shown on pathological analysis. There was an extension to the capsule without penetration into the pericapsular fat, as well as an extension into the hilum without invasion of the renal vein (T2 Nx). Resection margins and metastatic workup were negative. He underwent a routine surveillance program. Ten months after the operation, a right pleural metastasis was confirmed by needle aspiration. He received an intermediate dose of IL-2 that was not well tolerated and subsequently discontinued. He was then treated with sorafenib, but subsequently developed pulmonary progression and appearance of bone lesions. Treatment with sunitinib was initiated at a dose of 50 mg daily 4 out of every 6 weeks. Initial regression was documented in the lung and bone disease remained stable radiologically.

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Hypothyroidism occurred rapidly after initiation of therapy and was treated with replacement hormones. The dose was reduced to 37.5 mg due to palmoplantar toxicity 4 months after starting therapy, followed by a second dose reduction to 25 mg. Stable disease in the bone and lungs was documented radiologically at 37.5 mg and 25 mg doses.

Later, with sunitinib 25 mg, a palpable and painful mass in the right flank developed.

Computed tomography (CT) with intravenous contrast showed a lytic mass in the chest wall, next to the liver, destroying several ribs. This mass had a thickness of 6 cm and a bi-dimensional diameter of 10 cm x 7.5 cm.

CT-planned radiotherapy was administered to this mass via two tangential fields, similar to chest wall irradiation after mastectomy. A single dose of 8 Gy was given and repeated 8 weeks after the initial treatment. The mass disappeared clinically nearly completely and was asymptomatic already before the second treatment.

Sunitinib was later discontinued due to a hemorrhagic event following the introduction of low molecular weight heparin (LMWH) for deep vein thrombosis. Upon cessation, disease flared up in the lung and the reintroduction of sunitinib at 25 mg resulted in tumor regression. The bone disease was stable at other sites and did not increase following sunitinib cessation.

Discussion

Sunitinib is a multi target angiogenesis inhibitor. It is an inhibitor of tyrosine kinase and of several vascular endothelial- and platelet-derived growth factor receptors. It is approved for the treatment of metastatic renal cell carcinoma and imitinib-resistant gastrointestinal stromal tumors. In a randomized trial of patients with metastatic renal cell cancer, it showed superior progression free survival rates compared to interferon-α.[1]

The patient's disease responded well to sunitinib therapy, except for one bone lesion which continued to progress. Radiation therapy was therefore initiated to address disease progression under sunitinib therapy.

Traditionally, the predominant opinion of the radiation oncology community is that renal cell carcinoma is relatively radio resistant although clinically, there are significant subjective and objective response rates with the use of palliative radiotherapy.[2] This notion of radio resistance stems mainly from the limited response of brain metastases from RCC to RT.[3,4] More recent publications show a better response with radiosurgery[5,6] highlighting the importance of increasing the biologically effective dose (BED). The principle of BED is used to compare different radiation treatments and their impact on both tumors and normal tissues.

In their retrospective analysis, DiBiase et al[7] reported the influence of BED on partial or complete response in respect to symptom palliation in 107 patients with RCC. The median biologically effective dose was 50.5 Gy (range 14.4 to 74.8), using an α/β of 10. The patient in this report was treated with two doses of 8 Gy each. With the BED formula from DiBiase et al, the BED would only be 16 Gy, which is very low. A possible explanation for the surprisingly good response of our patients to radiotherapy is that sunitinib has a radio sensitization effect. Experiments in mice with sunitinib have shown a synergistic enhancement of the effect of radiation on tumor vascularization.[8] One could hypothesize that the sunitinib concentration at that site was too low to have a direct effect on the metastasis, but was sufficient to result in a radio sensitizing effect.

The hypothesis of a radio sensitization effect is supported by a report by Gay et al.[9] They described a case of complete response to hypofractionated radiotherapy (13 x 3.75 Gy = 48.75 Gy) with electrons for cutaneous metastasis. Sorafenib, a new multitargeted kinase inhibitor (Nexavar) was started 1 week after radiotherapy. A possible synergistic or radio sensitization effect and the safety of a combination of radiotherapy and a TKRI is also studied in currently opened trials. The National Cancer Institute clinical trial database (www.cancer.gov/clinicaltrials/search), currently lists two trials investigating the combination of a TKRI (sorafenib) and radiotherapy on metastatic renal cell carcinoma.

There are different rationales for combining antiangionetic agents such as sunitinib with radiotherapy. However if indeed there is a synergistic effect between radiotherapy and the kinase inhibitors, then one must be concerned with increased radiation induced toxicity, as experience has shown with thalidomide, an antiangiogenic, immunomodulatory, antiproliferative, and proapoptotic agent.[10]

In conclusion, there is preclinical and clinical evidence of a synergistic effect when sunitinib is administered together with radiotherapy. For better symptom palliation, further research needs to be done to find the ideal sunitinib and radiation dose for concomitant treatment. □

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