Title

A phase I/II trial of hafnium oxide nanoparticles activated by radiotherapy in hepatocellular carcinoma and liver metastasis

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Category

Liver cancer

Background

Management of hepatocellular carcinoma (HCC) and liver metastasis (mets) requires complementary expertise of multiple specialties. Treatment decisions are increasingly complex and physicians must face a wide range of underlying liver dysfunctions and concomitant malignancies. Among available treatments, stereotactic body radiation therapy (SBRT) is well-tolerated. Yet, like with all radiation therapy (RT) techniques, the energy dose deposit needs to be maximized in tumor cells without affecting the surrounding healthy tissues. For such purpose, nanoparticles of hafnium oxide, NBTXR3, were designed to effectively absorb ionizing radiation and augment the dose deposited within the tumor cells only when activated by RT. NBTXR3 is characterized by one single administration before the first RT session and it fits into existing standard of care with no change in patient treatment schedule protocol or equipment occupancy. It is currently evaluated in a phase I/II clinical trial bringing together multiple medical fields to introduce the use of NBTXR3 with SBRT in patients with HCC or liver mets [NCT02721056].

Methods

The trial follows a 3+3 dose escalation design at dose levels of NBTXR3 corresponding to 10%, 15%, 22%, 33% and 45% of the baseline tumor volume. Treatment is performed as a single intralesional or intraarterial injection followed by SBRT (45Gy / 3 fractions / 5 to 7 days) on patients with HCC with/without Portal Vein Tumor Thrombosis or liver mets. As SBRT is not supported by all French hospitals, the coordination of two institutions was needed in managing the patients course. This study aims primarily at identifying the Recommended Dose and of early Dose Limiting Toxicities (DLTs). Secondary endpoints include target lesions investigator assessment by mRECIST via MRI.

Results

The first two dose levels at 10% and 15% are completed with 6 and 4 patients respectively. Two patients are currently included at the third dose level at 22%. All currently recruited patients were treated by intralesional injection. No early D LTs nor adverse events (AE) related

to NBTXR3 were observed. One grade 2 malaise and two grade 3 abdominal pain AEs were reported to be related to the injection procedure. No serious adverse events related to NBTXR3 nor to the injection procedure were observed. Dispersion and permanence assessments by CT scan confirmed NBTXR3 to stay within the tumor without negatively impacting liver functions nor the reliability of the image-guided radiation therapy. Investigator assessment on target lesions by mRECIST via MRI resulted with the following best observed responses of target lesions to date in 7 evaluable patients: 3 complete responses, 3 partial responses and 1 stable disease.

Conclusion

Overall, NBTXR3 is well tolerated with a positive safety profile. Indeed, NBTXR3 could constitute an encouraging perspective for patients vulnerable to liver complications. The success of the cooperation between different medical disciplines and several sites paves the way to an innovative mean of managing multidisciplinary affections. Parallelly, NBTXR3 is also evaluated in 5 other clinical trials, including a phase II/III in soft tissue sarcoma [NCT02379845] and phases I/II for head and neck [NCT01946867; NCT02901483], prostate [NCT02805894] and rectum cancers [NCT02465593].

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