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Title

Hafnium oxide nanoparticles activated by radiotherapy: an innovative approach for the treatment of liver cancers

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Purpose/Objectives

Radiation oncology technological development is principally focused in improving the precision of radiotherapy (RT) and reducing unwanted irradiation to normal tissues. There is an unmet medical need into ameliorating the energy dose deposit within tumor cells without increasing the dose received by surrounding healthy tissues. In response, hafnium oxide nanoparticles, NBTXR3, were developed. Only when activated by RT, NBTXR3 increases the probability of interaction with incoming radiations to augment the energy dose deposition within tumor cells leading to their death.

Their use is particularly relevant in the management of liver cancers, notably hepatocellular carcinoma (HCC) and liver metastasis (mets). This population is heterogenous and difficult to treat due to the presence of underlying liver dysfunction and concomitant malignancies.

NBTXR3 activated by stereotactic body radiotherapy (SBRT) is currently evaluated in this population in a phase I/II study [NCT02721056]. The multidisciplinary aspect of the study, emphasized by the plurality of liver affections, leads physicians from multiple backgrounds to combine their expertise in managing patient's course.

Materials/Methods

11 patients (pts) suffering from primary HCC (with/without portal vein tumor thrombus) or liver mets were included and treated with a single intralesional or intraarterial injection of NBTXR3 followed by SBRT (45 Gy / 3 fractions / 5 to 7 weeks). As SBRT is not supported by all French hospitals, in some cases the coordination of two institutions was needed in managing the patient's course.

The study was designed as a 3 + 3 escalation dose with tested dose levels at 10%, 15%, 22%, 33% and 45% of baseline tumor volume. Primary endpoints include the determination of the recommended dose and of early dose limiting toxicities (DLT). Secondary endpoints include evaluation of NBTXR3 residency and/or presence of leakage and efficacy per mRECIST response.

Results

Intralesional injections were successful and radiotherapy was delivered as planned with no early DLT, AE nor SAE related to NBTXR3 for dose levels 10% (6 pts), 15% (4 pts) and 22% (1 pt). So far, two AEs (malaise, grade 2; abdominal pain, grade 3) related to the intralesional injection were reported at 10% and 15%.

The overall best response assessed by local assessment of the target lesion by mRECIST via MRI resulted with 3 CR, 3 PR and 1 SD out of 7 evaluable patients. Importantly, NBTXR3 nanoparticles did not impact the reliability of image-guided RT.

Conclusions

NBTXR3 was well tolerated and comes with a promising safety profile. Recruitment of dose level 22% is ongoing. This study successfully demonstrated the feasibility of a complex multidisciplinary coordination for 2 different important indications in liver oncology.

NBTXR3 is also evaluated in 5 other clinical trials, including a phase II/III in soft tissue sarcoma (STS) [NCT02379845] and phases I/II for prostate [NCT02805894], head and neck [NCT01946867] and rectum cancers [NCT02465593].

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