

MIYATAKE-2: A phase II clinical trial using accelerator-based BNCT system for refractory recurrent high-grade meningioma

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Background: For these couple of decades, nuclear reactors were used for BNCT as a neutron source. Instead of nuclear reactors, recently accelerator-based neutron sources (ABNS) have been developed for clinical trials to obtain on-label use, i.e., new drug approval. We have done the phase 2 clinical trial with cyclotron-based ABNS system for recurrent malignant gliomas, of which results were applied in this meeting as another talk. On the other hand, recurrent high-grade meningiomas after X-ray treatment showed 5.2 months as progression free survival (PFS) and only 24.6 months as overall survival (OS) from the literatures. Recently we have applied reactor-based BNCT for 46 cases of refractory and recurrent high grade meningioma (HGM, WHO grade 2 or 3). All cases showed good tumor shrinkage with good local control. This patient number is approximately a quarter of cases of brain tumors treated by reactor-based BNCT. Study Purpose: Based on these situations, we proposed “A phase II clinical trial using accelerator-based BNCT system for refractory recurrent high grade meningioma” for Japan Agency for Medical Research and Development (AMED) which is similar to NIH in USA.

Study Design: Pharmaceutical and Medical Devices Agency (PMDA) in Japan which is a counter part of FDA in USA suggested the importance of randomized clinical trial (RCT) even for this exploratory clinical trial for rare tumors, such as HGMs. Along to this suggestion, we prepared 2 study groups, BNCT test treatment group and control best supportive care group. PFS was set-up as primary endpoint and OS was set-up as secondary endpoint. To diminish ethical problems of this RCT, rescue BNCT is permitted for control group patients, if they showed progress disease during the observation period. 2-dimensional modified Macdonald criteria is adopted for assessment. Hypothesized PFS of treatment group and control group was 5 months and 24 months, respectively. Fortunately our proposal was adopted by AMED and the trial started in August 2019. Methods: Twelve and 6 subjects will be included for this trial as test treatment BNCT group and control group, respectively. Patients eligibility criteria is as following, recurrent HGM after some radiotherapy (less than 65 Gy as fractionated X-ray treatment, daily 2Gy fraction), aged more than 20 and less than 75. KPS should be more than 60%. SPM-011 as BPA is administrated 500mg/kg in 3 hours intravenously, 200 mg/kg an hour for 2 hours prior to neutron irradiation and 100mg/kg an hour during neutron irradiation. Cyclotron-based ABNS system is used for neutron source. Neutron-irradiation time is determined not to exceed to 7.5 Gy-Eq for scalp dose which was referencing preceding phase I trial for malignant gliomas.

Progress of this trial: As of April 2020, 4 subjects were included, 3 for BNCT treatment group, 1 for control best supportive care group.

Conclusion: In my talk, let me present our clinical data of reactor-based BNCT for high grade meningiomas and clinical trial design of this accelerator-based BNCT in detail. And if possible let us introduce the interim report of this clinical trial in the meeting.