

WITTIG-1: Clinical trial strategies for BNCT

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In BNCT two different components have to come together namely low-energy neutrons with an activating agent that is harmless except in the presence of the neutron radiation. The radiation dose applied by the neutron field is low, except in the presence of the agent. Both modalities are not effective when applied alone. Until a few years ago, the only possible radiation source was a research reactor. At no time was it possible to commercially distribute research reactors for BNCT, so individual authorization was required, but not certification as a medical device. The situation now has changed and accelerator-based neutron sources with a high current proton accelerator, a target and a Beam Shaping Assembly (BSA) are marketed and have to be certified as a medical device. Nowadays in many countries, such certification includes a clinical trial. Clinical studies with BNCT have to demonstrate to the regulatory authorities that this new modality can be safely used for routine clinical applications. The trials have to be conducted in accordance with the established standards of evidence-based medicine. In particular, they have to follow the principles of the Declaration of Helsinki, and good clinical practice. The well-established trial system for drugs consists of phase I trials to evaluate the maximum tolerated dose and determining the spectrum of side effects and unexpected toxicities. International guidelines for evaluating medical devices such as European Medical Device Directives 93/42/EEC and 2007/47/E and Guidelines on Medical Devices in MEDDEV 2.7.1, Rev 4 do not mention how such clinical trials have to be designed because of the big differences between different medical devices. However, as long as a new radiation source is tested with an existing and accepted drug, the difficulties to design such trial are manageable.

Another degree of complexity will be the introduction of a new boron carrier into clinical use. Up to now, the pharmaceutical industry did not develop new drugs for BNCT. The only drug that currently is marketed in Japan, BPA, is a molecule synthesized in the 50ies of the last century and first used for BNCT some 30 years ago. A classical Phase I trial for a drug that has to be given in high quantity (grams), non-toxic in animals but with unknown toxicity in humans and without potential beneficial effects is impossible to realize. Realistic clinical trial strategies have to be found that will allow for the testing of new drugs for BNCT, which have no certifiable activities without irradiation. Using surrogate endpoints like boron uptake in tissues for patients, who undergo surgery for the targeted tumor might be difficult but is not impossible [1,2]. The problem gets better, if patients can be irradiated with the new drug. In such situation, there is at least a potential benefit for them. Phase II and Phase III trials have a different intention and will focus on the effect on a defined tumor. With such trials, new indications for BNCT can be established.

All of these different aspects should be integrated in a well-defined system. Up to now, for such an integral concept only a few suggestions exist [3,4].

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