The BNCT facility at the HFR Petten: Quality assurance for reactor facilities in clinical trials

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Abstract. The first clinical trial in Europe of Boron Neutron Capture Therapy (BNCT) for the treatment of glioblastoma was opened in July 1997. The trial is a Phase I study with the principal aim to establish the maximum tolerated radiation dose and the dose limiting toxicity under defined conditions. It is the first time that a clinical application could be realised on a completely multi-national scale. The treatment takes place at the High Flux Reactor (HFR) in Petten, the Netherlands, is operated by an international team of experts under the leadership of a German radiotherapist, and treats patients coming from different European countries. It has therefore been necessary to create a very specialised organisation and contractual structure with the support of administrations from different countries, who had to find and adapt solutions within existing laws that had never foreseen such a situation. Furthermore, the treatment does not take place in an hospital environment and even more so, the facility is at a nuclear research reactor. Hence, special efforts were made on quality assurance, in order that the set-up at the facility and the personnel involved complied, as closely as possible, with similar practices in conventional radiotherapy departments.

1. INTRODUCTION

The first clinical trial in Europe of Boron Neutron Capture Therapy (BNCT) for the treatment of glioblastoma was opened in July 1997 at the High Flux Reactor (HFR) in Petten, the Netherlands [1,2]. The first patient was treated in October the same year and currently, 10 patients have received treatment. The trial is a Phase I study with the principal aim to establish the maximum tolerated radiation dose and the dose limiting toxicity under defined conditions. It is the first time that a clinical application could be realised on a completely multi-national scale, whereby a unique facility available for BNCT is localised in one country (The Netherlands) and is operated by an international team of experts under the leadership of a German radiotherapist, treating patients coming from different European countries. It has therefore been necessary to create a very specialised organisation and contractual structure with the support of administrations from different countries, which had to find and adapt solutions within existing laws that had never foreseen such a situation.

It was apparent in the early stages of setting up the project, especially during many of the discussions with the Health authorities that quality, and certainly Quality Assurance (QA), would become a critical aspect of the whole trial. This was particularly the case with BNCT, as not only was it a new, experimental treatment about to be performed for the first time in

The Netherlands, and indeed Europe, but it would be performed in a non-hospital environment and in particular at a nuclear research site. It was necessary therefore to comply, as closely as possible, with similar accepted practices in conventional radiotherapy departments.

2. RADIOTHERAPY ASPECTS ON QUALITY ASSURANCE AND SAFETY

The council directive on health protection 97/43/EURATOM (based on recommendation of ICRP-60) requires explicitly appropriate QA programmes for performance and safety of radiotherapy units, including testing of performance characteristics on a regular basis.

Firstly, we should remind ourselves that for clinical trials, Quality Assurance means all those planned and systematic actions that are established to ensure that the trial is performed and the data is generated, documented (recorded) and reported in compliance with Good Clinical Practice (GCP) [3,4] and the applicable regulatory requirements. Furthermore, in the context of these actions, we should distinguish between Quality Control (QC), which are the operational techniques and activities with the QA system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Regarding GCP, this is the standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that rights, integrity and confidentiality of trial subjects are protected. As part of the GCP guidelines, Standard Operating Procedures (SOPs) are written which give the detailed instructions to achieve uniformity of the performance of each specific function.

3. NUCLEAR ASPECTS ON QUALITY ASSURANCE AND SAFETY

Conducting a clinical trial at a nuclear research centre does not impose in itself that a QA system fulfilling GCP guidelines must be performed. Nuclear installations inevitably themselves have their own QA systems. At the HFR, a Quality and Safety policy exists to maintain the key position of the HFR amongst research reactors worldwide, which can only be achieved and maintained by remaining at a high level of safety and quality in all aspects of operation of the reactor. The quality system is based, amongst others, on the principle of ISO 9001 and the environmental principles in ISO 14000. As part of the QA system, the Quality manual of the HFR describes the quality system and refers to the quality guidelines, procedures and working instructions as collated in the IAM Quality system, the Dutch Nuclear Safety Rules, the QA guidelines of the IAEA, and the HFR Technical Operational Guidebook.

Consequently, when compared, there are inevitably many overlapping similarities existing in both the medical and nuclear QA systems. Hence, the requirement to fulfil GCP for clinical trials at nuclear installations is not that peculiar. As a result, BNCT at Petten is performed respecting European, Dutch and whenever possible, German rules of safety and quality assurance for nuclear research reactors, for radio-protection, for radiotherapy units and for clinical trials [5]. In particular, quality assurance of safety provisions and functional performance characteristics conform to the most recent concepts and regulations of IEC publications and/or DIN standards for medical electron accelerators [6–9] and for treatment planning systems [10] or, as far as is possible, transferred analogously.

All relevant procedures concerning the execution of the clinical trial are described in a file of Standard Operation Procedures. The file of SOPs contains step-by-step descriptions of

some 55 procedures, including all nuclear activities, such as, for example, the reactor hall evacuation in case of a nuclear incident. A copy of the SOP file is in possession of each participant involved in the trial.

4. THE BNCT IRRADIATION FACILITY AT PETTEN

Treatment of the patient takes place at the HFR [11], located at the Joint Research Centre in Petten, The Netherlands. The HFR is a 45 MW, materials testing reactor, with the prime objective to perform experiments on nuclear fuels and materials destined for the European civil nuclear power programmes. In recent years, the reactor has increased its area of application into medicine, in particular radioisotope production, as well as BNCT. For BNCT, a specially designed filtered beam tube and irradiation room was built at one of the eleven horizontal beam tubes located around the reactor [12].

In designing, implementing and reviewing the development of the facility, the required work was carried out in conformance with accepted standards in QA and QC. The design of the whole facility was reviewed critically by the local Reactor Safety and Experimental Assessment Committees, who have the mandate to judge a facility on both its nuclear and conventional safety aspects, including reactor safety and radio-protection of the personnel. The working environment was reviewed by the appropriate regulatory body at the Ministry of Social Affairs (SZW), who assessed the facility on the basis of site-visits and documentation [13] which described the facility in detail, including the justification for BNCT, its conformance with the ALARA (as low as reasonably achievable) principles of radiation protection and the organisational structure, where the medical and radio-protection responsibilities are clearly defined. The facility also underwent a local quality audit, as part of the JRC's mission to become a licensed Quality Management (QM) site according to ISO 9001 during 1999. Finally the facility had a site-visit by an independent physician with personal expertise in clinical applications of BNCT.

The step-by-step procedure in developing such a QA system is given in ISO9001. For an experimental facility, the structure is well defined. When medical procedures, and in particular BNCT procedures, are required, the written and executed procedure is an adaption of the written standard.

For a BNCT facility the procedures described in the following sections are based on the experience at Petten. Whist similarities elsewhere will exist, differences or even non-applicability of some of the procedures will occur.

4.1. Dosimetry

Dosimetry guidelines, as followed in conventional treatment centres, apply to photon, electron or fast neutron facilities. For BNCT facilities, where an epithermal neutron beam is used, the beam (in air) includes fast neutrons (>10keV) and gamma rays. The latter comes from both the beam itself (reactor gammas) and from activation of the in-beam material [13]. In human tissue, containing boron-10 compounds, the beam produces effectively four main dose components, all with different biological effectiveness: the boron neutron capture absorbed dose, the nitrogen neutron capture absorbed dose, the fast neutron absorbed dose and the gamma ray absorbed dose.

Furthermore, the neutron beam emanates from a reactor, which in the case of the HFR, as a strict operating schedule, running 24 hours per day for eleven cycles of 4 weeks each, per

year. Hence due to burnup of the reactor fuel, the intensity of the beam over the scheduled 4 weeks cycle reduces by some 4–5%. Also, the intensity of the beam at the start of each cycle may vary by some ±4% per cycle, due to experimental loading changes in the reactor. Hence, quality assurance of the beam during treatment must follow a strictly controlled procedure, which includes the following steps:

- free beam measurements on a monthly basis, using a multi-foil packet consisting of 12 activation foils,
- on the first day of the treatment week (each patient receives a fraction of radiation on four consecutive days), reference phantom measurements are performed using activation foils, twinned ionisation chambers and a pn-diode,
- the measurements are used to calibrate the on-line monitors (see next section),
- on succeeding days of treatment, the reference phantom measurements are repeated using the pn-diode, twinned ionisation chambers and the in-beam monitors, which are all normalised to the first day's measurements.

Following the QA system, as well GCP, all measurements are written down, controlled and countersigned by the responsible person, documented and later archived. Despite the complexity associated with BNCT dosimetry, QA procedures applied for BNCT infer less radiation and operational procedures than for conventional radiotherapy. Furthermore, reproducibility in BNCT is equivalent with medical accelerators, whilst all safety requirements and equipment functions, including against stray radiation are equivalent.

4.2. Beam monitoring and beam shutter control

The QA concept applied for the BNCT beam, is the same as that established for conventional radiotherapy purposes, but adapted for the special situation at the reactor. All safety systems are backed-up by an independent second device acting in case of failure of the first. The beam monitoring system consists of four beam monitors: two ^{235}U fission chambers (neutron counters) and two GM-tubes (gamma ray counters), which are located in the fixed beam collimator, downstream from the main beam shutter and before the sliding gamma shutter. The automatic opening and closing of the beam shutters is controlled by the fission chambers, according to the pre-set number of monitor counts which correspond to the required boron dose delivered at the DGIP (dose group identification point) [2] in a patient. Both fission chambers are pre-set to close the shutters, which are automatically triggered when the target counts are reached. Fission chamber nr.1 acts as the principal counter, with nr.2 as the back-up. Both chambers, as well as the GM-tubes, are monitored and counts and count rates displayed on two independent computer systems. As an additional back-up for beam shutter closure, a timer is available, with a pre-set time at 2% above the given irradiation time. If called into use, closure of the beam shutters is automatically triggered. If necessary, the beam shutters can be closed by means of a push-button on the beam shutter operations panel. If this fails, due to electrical failure, the beam shutters can also be closed by means of manual mechanical devices [14]. As a last resort, the beam operator has the mandate to instruct the reactor operators to scram the reactor.

The above description is given as an example of the working philosophy of one of the main components in the overall BNCT facility. Similar detailed descriptions exist for other principal components, but for brevity, will not given here.

4.3. Radiation protection

Radiation protection procedures follow the national and international QA systems where responsibility is the most important issue. To conform with the Dutch regulations on radio-protection, an authorised Radio-Protection Committee for BNCT has been formed. The committee has the prime task to review and advise, on a half-yearly basis, the radio-protection methods used for BNCT. If need be, this advice is transmitted to the appropriate regulatory authority.

4.4. BNCT treatment planning

As part of the overall treatment planning procedure, supplementary use is made of the INEEL treatment planning program [15], which is located on 2 separate SUN workstations at JRC. The QA system provides for the necessary documentation, etc. as given in the above sections. As part of the QA system, a quality control procedure for the program involves calculations on two standard test cases, i.e. a standard patient and standard phantom, which are calculated to check for possible non-conformance. The cases are chosen in such a way that all the essential parts of the program are used. At defined periods, the versions on both workstations, whether updated or not, are run for the two standard test cases. A control procedure is followed and performed each time a new version of the program is installed. The procedure includes comparative calculations, back-up steps and SOP updates.

For the patient plans, each treatment plan is calculated in Petten and presented, discussed and agreed at the radiotherapy department of Essen University during their daily audit on treatment planning.

4.5. Patient positioning system

The preparation for the treatment planning is done at the referral hospital, including making of the positioning mask. The CT images are transferred to Petten, where the treatment planning calculations give the geometry of the incident beam to the patient, as well as the beam centre-line entrance and exit points. To position the mask in the required position, a system has been developed based on the QA principle of reproducibility. The frame utilises an open, aluminium framework in which the mask is placed. The step-by-step procedure is described in the relevant SOP, the positioning can be accurately and quickly controlled by the radiotherapist [16].

4.6. Prompt gamma ray analysis

The mean blood-boron concentration during the treatment of the patient is determined by means of prompt gamma ray analysis [17], which is located at Petten on a neighbouring beam tube (HB7) in the reactor hall. A quality control of the facility is performed on the first day of each treatment week, when the resolution of the detector is checked using a ^{60}Co source, and the function and accuracy of the entire system is checked using calibration samples. On the days of patient treatment, the resolution of the detector is checked again, and the set-up is calibrated using standard samples. One blood sample per patient and one calibration sample are later validated by ICP-AES, available at Petten. Again a documented procedure is strictly followed.

4.7. Training of the staff

Prior to treatment of the first patient, a training programme was carried out and repeated on a regular basis, whereby all procedures and actions necessary to perform BNCT have been simulated in "dummy runs". Special attention was paid to emergency situations including both technical and medical failures, such as a reactor hall evacuation emergency and a simulated cardiac arrest of the patient. With respect to a QA system, it has to be demonstrated that staff following a specific training schedule related to the needs of the experiment, i.e. trial.

5. CONCLUSION

The first demonstrations of BNCT in the USA were thwart with danger and were damaging to the patient. The fact that the clinical trials, also here in Petten, take place in a nuclear research reactor, which apart from being conducted in a non-hospital environment, conveys to some people, possible additional dangers. It is therefore of the utmost importance that special attention is given to safety, beyond normal rules, and to the training of staff. This is most poignant when demonstrable strict quality assurance procedures exist, offering guaranteed reliable and safe functioning of the treatment.

Despite the fact that guidelines for QA on health protection may appear only to be applicable to medical applications, they are based on the same principles of QA systems in general. Hence, when compared, there are inevitably many overlapping similarities existing in both the medical and nuclear QA systems. The requirement to fulfil GCP for clinical trials at nuclear installations is therefore not that peculiar. Thus, QA procedures for BNCT at nuclear installations can be, and should be, readily implemented.

ACKNOWLEDGEMENTS

The clinical trial is financially supported by the European Commission's Biomedicine and Health Research Programme (BIOMED II).

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