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Horizon Scanning Technology Prioritising Summary

Boron neutron capture therapy for cancer treatment

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PRIORITISING SUMMARY

REGISTER ID: **000341**

NAME OF TECHNOLOGY: **BORON NEUTRON CAPTURE THERAPY FOR CANCER TREATMENT**

PURPOSE AND TARGET GROUP: **CANCER THERAPY**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☒	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☐	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☒	No	
☐	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Japan	✓		
Sweden	✓		
Italy	✓		
USA	✓		

IMPACT SUMMARY:

Boron neutron capture therapy (BNCT) involves the selective, radiation-based destruction of a variety of malignant tumours, but mainly cancers of the head and neck. This technology would be limited to use in tertiary hospitals that have access to a neutron source, such as a nuclear reactor. No evidence was found indicating this technology has entered the Australian health care system.

BACKGROUND

Boron has two naturally occurring isotopes boron-10 and boron-11, which is the most common natural isotope. Boron-10 is non-radioactive and is the isotope used in boron neutron capture therapy (BNCT). BNCT is based on the selective uptake of non-radioactive boron compounds, delivered via intravenous injection, by a tumour, and the subsequent irradiation of the area with an appropriate neutron beam. When

compounds containing boron-10 are irradiated within the body with low-energy neutrons, the boron absorbs the neutrons and decays *in situ* releasing high-energy α particles and lithium-7 nuclei. These particles can only travel a very short distance and as such release their damaging energy directly to the tissue that contains the boron compound. This has two advantages. Firstly, the dose of radiation given in the neutron beam can be quite low and, secondly the local decay and action means that the surrounding healthy tissue is spared. The most important issue for BNCT and the successful treatment of tumours is the delivery of the boron bearing compounds to the tumour site. To be effective the boron compounds must achieve a concentration of 20μg per gram of tumour. The current generation of boron compounds are taken up systemically but have some small margins of tumour selectivity, i.e. the tumour will have a greater concentration than the blood or surrounding normal tissue. More selective boron compounds, which specifically target tumour cells, such as monoclonal antibody fragments and low-molecular weight compounds targeted at specific tumour markers are being developed. The boron compounds most widely used in BNCT are sodium borocaptate and boronophenylalanine.

To date the main types of cancers treated in trials with BNCT have been advanced gliomas, and melanomas (either primary melanomas or cerebral metastases of melanomas). Head and neck, and liver cancers have also been recently treated with BNCT (Barth et al 2005).

CLINICAL NEED AND BURDEN OF DISEASE

There are no accurate Australian data for specific types and stages of the cancers potentially treatable by BNCT. In 2003, the number of cases for the main cancers currently treated with BNCT were: 2,476 head and neck cancer cases; 9,524 melanoma cases; 1,360 brain cancers; and 890 liver cancers, giving a total of 13,563 cases. Only some of the cancer cases in these broad categories would require treatment with BNCT, or are of the specific types treated so far with BNCT. These figures show the upper limit of numbers of patients who may require BNCT (AIHW 2007).

BNCT may be utilised for several cancers which are resistant to many, if not all, current cancer therapies available. For example, glioblastoma multiforme, a type of brain cancer, is resistant to surgery, chemotherapy, radiotherapy, immunotherapy, and gene therapy. Advanced melanoma and metastases of melanoma may also be difficult to treat (Barth et al 2005).

DIFFUSION

No evidence was found to indicate this technology had entered the Australian health care system.

COMPARATORS

The current standard therapies used against the wide array of cancers potentially targeted by BNCT include: for gliomas: surgical resection of the tumour, followed by chemotherapy and radiotherapy; for melanomas: mainly surgery; for liver cancer: surgical resection or liver transplant; and for head and neck cancers: surgical resection followed by combined chemotherapy and radiotherapy (Bernier 2007; Blazer et al 2007; Garbe & Eigentler 2007; Miyazaki et al 2007; See & Gilbert 2007; Spriano et al 2006).

SAFETY AND EFFECTIVENESS ISSUES

The effectiveness of BNCT has been investigated in several small studies to treat various different cancers. However, the majority of patients included have advanced-stage, treatment refractory cancers where no other therapeutic options exist.

Optimisation of the dose of radiation given to the patient is important for balancing the competing issues of maximal dose to the tumour and minimal dose to the healthy tissue. A small study, which used sodium borocaptate as the boron delivery agent, involved 19 patients with malignant glioblastoma (Kageji et al 2006) (level IV intervention evidence). The reported dose was 26 Gy[1] for the gross tumour volume and 16 Gy for the clinical target volume. Higher doses of radiation delivered during BNCT were significantly associated with an increased survival time. A second study investigating the BNCT treatment of gliomas intraoperatively also reported low toxicity and good results in nine high-grade glioma patients, with a reported median survival of greater than two years. The four tumours remaining after resection showed a complete (n=2) or partial response (n=2) six months after BNCT (Yamamoto et al 2004) (level IV intervention evidence).

The recurrence of tumours at sites previously treated with radiation poses a significant problem in the clinical management of cancer patients. A small study treated 12 patients with BNCT, using the boron delivery agent boronophenylalanine-fructose (Kankaanranta et al 2007) (level IV intervention evidence). All patients had experienced a recurrence of head and neck cancer at a site previously treated with conventional radiation. Ten patients responded to the BNCT therapy with a median response time of 12.1 months. Tumour size stabilisation was reported in the remaining two patients at 5.5 and 7.6 months. Four of the patients showed no recurrence of the tumour between 12.8 and 19.2 months, indicating this is a promising treatment for otherwise untreatable cancers. A second study on recurrent head and neck cancer in six patients also reported very promising results for this difficult to treat malignancy (Kato et al 2004) (level IV intervention evidence). A pair of boron compounds, boronophenylalanine and sodium borocaptate was injected intravenously, and the boron-10 concentrations in the tumours were 1.8 to 4.4 times the normal tissue

[1] Gy = gray (unit), SI unit of absorbed radiation

concentration for squamous cell carcinoma, sarcoma, and parotid tumour. Reductions in tumour size ranged from 6 to 46 per cent of their original volume. Large tumours (average 315 cm^3) showed 46 to 100 per cent reductions in their size.

Most protocols for BNCT use thermal neutrons as these are best captured by boron-10, yet as thermal neutrons they lack penetrative power. Epi-thermal neutrons[2] which can penetrate further into tissue can be absorbed by boron-10 once they fall into the thermal range. Epi-thermal neutrons therefore have the advantage of penetrative power while still being able to be absorbed by boron-10. A study investigated the ability of epi-thermal neutrons to function in BNCT of 13 glioma patients. The investigators used boronophenylalanine and sodium borocaptate as the boron delivery compounds. Combining both these compounds, which have different metabolic profiles, allows an increase in the accumulation of boron-10 in the tumour, resulting in an increase in neutron absorption. From a mean tumour volume of 42.3 cm^3 before BNCT, there was a mean reduction of tumour volume of 46.4 per cent (range 17.4-71%) at two to seven days post treatment. At a later follow-up the mean volume-reduction was 58.5 per cent (range 30.3-87.6%). In eight of the twelve patients followed up, more than 50 per cent of the lesions had disappeared. The successful use of epi-thermal neutrons indicates an expanded capability for BNCT extending its effective range deeper into the body (Miyatake et al 2005) (level IV intervention evidence).

With all radiation based treatment there is a large risk of damage to healthy tissues and associated sequelae. Several reports of BNCT safety data have been published and are summarised below.

The post-mortem examination of seven brains, of patients treated with BNCT (p-boronophenylalanine based), by microscopic or immunological analysis showed no evidence of radiation induced damage in the normal tissue, yet there was localised control of the glioblastoma multiforme at the site where BNCT treatment was targeted. These seven patients were part of a group of thirty who were treated with BNCT (Stenstam et al 2007) (level IV intervention evidence). A second study investigated the safety of BNCT by comparing 35 BNCT-treated subjects with brain or, head and neck tumours to subjects treated for thyroid cancer with radioiodine. The frequency of micro-nucleated (damaged) T-lymphocytes in the peripheral blood of both groups was assessed. While the BNCT subjects showed an increase in micro-nucleated T-lymphocytes, the *frequency* of micro-nucleated cells was three to five-fold lower than in the radioiodine treated subjects. This may indicate that BNCT is less damaging than existing standard cancer therapy (Kinashi et al 2007) (level IV intervention evidence).

[2] Epi-thermal neutrons have energy levels above thermal neutrons

COST IMPACT

No cost effectiveness data were found during the preparation of this summary. However, the cost impact of this technology would be extensive due to the need for a nuclear reactor to supply the neutron beam used in BNCT. Currently Australia has only one nuclear reactor, the OPAL reactor recently commissioned at Lucas Heights in New South Wales. This reactor is designed to produce neutron beams for scientific and medical research, although it is not clear if this is applicable to BNCT. The lack of neutron beam sources would make the cost of BNCT extremely prohibitive and available to very few patients.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were raised by the literature examined for this prioritising summary.

OTHER ISSUES

Due to the rare nature of the tumours treated with BNCT, data on its effectiveness and safety will only be generated sporadically and a lengthy period of accumulation of information will be necessary to assess the true impact of this technology.

SUMMARY OF FINDINGS

The studies identified in this prioritising summary were not of high quality and, as such, the conclusions must be taken as preliminary in nature. Despite this, the studies indicate that BNCT is a promising technology which appears to be able to safely and effectively treat very advanced and otherwise untreatable malignancies. Whether Australia has the infrastructure to support this technology is not evident and cost effectiveness data were not found.

HEALTHPACT ACTION:

BNCT is a promising technology that is rapidly advancing and improving, and may prove useful for the treatment of therapy refractive cancers. Studies, although restricted to small numbers of patients, have demonstrated an increased survival in patients. In addition, treatment with BNCT demonstrated no collateral damage to brain tissue. The Australian and New Zealand infrastructure capacity for the generation of neutrons is unclear at this current time, therefore HealthPACT recommended that this technology be monitored.

NUMBER OF INCLUDED STUDIES

Level IV intervention evidence	7

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SEARCH CRITERIA TO BE USED:

Boron Neutron Capture Therapy/ methods
Brain Neoplasms/ radiotherapy
Glioblastoma/ radiotherapy
Humans
Head and Neck Neoplasms/pathology/ radiotherapy
Radiation Dosage
Boron Compounds/therapeutic use
Glioma/complications/diagnosis/pathology/ radiotherapy