Applied Radiation and Isotopes ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

Clinical potential of boron neutron capture therapy for locally recurrent inoperable previously irradiated head and neck cancer

Diana Lim [a], Daniel SC Quah [b], Michelle Leech [a], Laure Marignol [a,*]

[a] Applied Radiation Therapy Trinity, Discipline of Radiation Therapy, School of Medicine, Trinity Centre for Health sciences, Trinity College Dublin, Ireland
[b] Department of Radiation Oncology, National Cancer Centre, Singapore

HIGHLIGHTS

- BNCT can prolong median overall survival.
- BNCT can be associated with severe adverse effects.
- BNCT may be comparable to chemotherapy-based regimens.
- BNCT may be comparable to re-irradiation techniques regimens in patients with low performance status.

ARTICLE INFO

Article history:
Received 19 January 2015
Received in revised form
23 June 2015
Accepted 25 July 2015

ABSTRACT

This review compares the safety and efficacy of boron neutron capture therapy (BNCT) in the treatment of previously irradiated, inoperable locoregional recurrent HNC patients and compares BNCT against the standard treatment of platinum-based chemotherapy. Our analysis of published clinical trials highlights efficacy of BNCT associated with mild side effects. However, the use of BNCT should be explored in stratified randomised trials.

1. Introduction

Patients with Locally Recurrent Head and Neck Cancer (LRHNC) have limited treatment options (Vermorken and Specenier, 2010). Optimal therapy has not been established and prognosis is generally poor (Tanvetyanon et al., 2009). Combination chemotherapy has been used, but results are far from satisfactory. The addition of EGFR inhibitors (cetuximab) conferred a median survival of 10.1 months, more than the 7.4 months of those who received chemotherapy only (EXTREME trial) (Vermorken et al., 2008; Vermorken and Specenier, 2010). Re-irradiation utilizing alternate techniques that can deliver a high tumouricidal dose while limiting normal tissue exposure has potential, and in this context, Boron Neutron Capture Therapy (BNCT) has also been explored. The first registered Phase II trial addressing the use of BNCT in Head and Neck Cancer (Kankaanranta et al., 2007, 2012) showed that it is effective in managing patients with LRHNC, but to date no studies have compared its potential to systemic therapy. This review aims to assess the clinical potential of BNCT in comparison to systemic therapies alone, systemic and radiation therapies and radiation therapy alone and thereby make observations on its potential for the improved management of these patients.

2. Materials and methods

Published BNCT studies were identified on MEDLINE using the following key words: “Head and Neck Neoplasms” [Mesh] AND “Neoplasm Recurrence, Local/radiotherapy” [Mesh] AND “Boron Neutron Capture Therapy”[Mesh]. RCTs were identified using the following MEDLINE search strategy: “Head and Neck Neoplasms” [Mesh] AND “drug therapy”[Subheading]) AND “Cisplatin/administration and dosage” [Mesh] AND “Neoplasm Recurrence, Local/drug therapy” [Mesh] AND “Clinical Trial, Phase III” [Publication Type]. The Cochrane Library was searched using the following key words: “head and neck neoplasm” AND chemotherapy NOT radiotherapy. Clinicaltrials.gov was searched using: “head and neck neoplasm” AND chemotherapy NOT radiotherapy. Seven phase I and phase II BNCT trials reporting the use of BNCT with intravenous administration of boron-carrier in patients with previously treated loco-regionally recurrent unresectable HNC were

* Corresponding author.
E-mail address: marignol@tcd.ie (L. Marignol).

http://dx.doi.org/10.1016/j.apradiso.2015.07.044
0969-8043/

identified. (Aihara et al., 2014; Ariyoshi et al., 2007; Kankaanranta et al., 2012; Kato et al., 2009; Kimura et al., 2009; Suzuki et al., 2014; Wang et al., 2011). The EXTREME phase III randomized controlled trial evaluating clinical outcomes of standard systemic therapy in this same category of patients was included to assess standard therapy (Vermorken and Specenier, 2010). The primary outcomes used to evaluate the safety and efficacy of BNCT for treatment of locally recurrent inoperable HNC patients were response rates (Complete and Partial Response), survival and incidence of severe acute adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTC) Grade 3-5). The secondary outcomes considered to compare BNCT to systemic therapies were response rate, survival and incidences of severe acute adverse events (NCI CTC version 3.0 Grade 3-5). The descriptions of original studies were assessed by using frequency, 95% confidence intervals and forest plots. Statistical heterogeneity across trials was assessed using the chi-squared (X^2) test and consistency between studies with the I^2 statistic (Higgins and Thompson, 2002). Fishers' exact tests were used to compare groups with respect to dichotomous end points (eg, response rates and toxicities). A *t*-test was performed according to the methodology described in (Hozo et al., 2005) to compare reported survival data between BNCT vs CTX, and between BNCT vs CTX/C225. All *P* values reported are two-sided. $P<0.05$ was considered statistically significant.

3. Results

3.1. Efficacy and safety of BNCT

Median overall survival of 13.1 and 9.7 months were reported (Kankaanranta et al., 2012; Suzuki et al., 2014). A survival time of up to 72 months was reported for one patient after receiving seven BNCT treatments over 6 years (Kato et al., 2009). Reports of progression-free survival ranged from 5.1 to 7.9 months (Kankaanranta et al., 2012; Suzuki et al., 2014). Reported response rates, based on the Response Evaluation Criteria for solid tumours, ranged from 61% to 100%. The heterogeneity of the treatment response between trials was significant (X^2 (5, $N=115$)=4.878, $p<0.05$). There was no evidence of statistical heterogeneity between trials (I^2 =17.9%, $p=0.3$). The weighted frequency of the response rate of these 5 trials was 72.1% (95%CI: [62.5–78.8]). All BNCT trials evaluated toxicity and severe adverse effects (Fig. 1). The incidence of Grade 3 toxicities was up to 53%, while that of Grade 4 was below 10%. Three treatment-related deaths were reported in a single trial (Suzuki et al., 2014). Mucositis was the most commonly reported toxicity.

3.2. BNCT vs standard chemotherapy

The overlay of the Kaplan–Meier curves from the two arms of the EXTREME trial (Vermorken and Specenier, 2010) and the Kankaanranta BNCT study (Kankaanranta et al., 2012) suggests that a proportion of patient treated with BNCT exhibit a better outcome than those receiving platinum chemotherapy alone or with combination of Cetuximab (Figs. 2 and 3). All 30 patients evaluated in the BNCT trial had inoperable head-and-neck cancers that had recurred locally with/without metastasis after surgery and prior conventional radiotherapy or chemoradiation therapy. The 442 patients included in the EXTREME trial had recurrent and/or metastatic squamous-cell carcinoma of the head and neck that were ineligible for local therapy. Patients from all groups received some form of treatment before disease recurrence and/or metastases. 53% of patients in the BNCT group had WHO Performance Status >1, similar to Karnofsky score (KPS) <80, in contrast to 11% and 12% of the CTX and the CTX+C225 group respectively. The median survival times for all patients offered BNCT, CTX/C225 and CTX were 13.1 months, 10.1 months and 7.4 months respectively (Tables 1 and 2). The survival advantage when compared to CTX/C225 and CTX were both considered statistically significant ($p<0.0001$). The hazard ratio (HR) was ~0.78 (95% CI: 0.5, 1.49) for BNCT vs CTX/C225 and ~0.57 (95% CI: 0.36, 0.9) for BNCT vs CTX. The percentage of patients who were alive at 1 year was higher for patients who received BNCT as compared to both CTX/C225 and CTX (60% vs 37% vs 29.5%). Long term survival (≥ 2 years) was also increased for patients treated with BNCT (30% vs <1%) and 18% of the patients treated with BNCT were still alive after 4 years. PFS was significantly improved in patients treated with BNCT than those receiving CTX/C225 and CTX ($p<0.0001$) The response rates for BNCT appear to be significantly better when compared to either arm of the EXTREME trial (both arms, $p=0.001$) (Table 1). While the percentages of Grade 3 toxicities were highest in the BNCT group (53%) and lowest in the CTX group (45%), Grade 4 side effects were significantly reduced in the BNCT group (3%) as compared to 31% of each of the CTX and CTX/C225 trials. The Grade 3 and 4 adverse toxicity profile for BNCT was significantly better than CTX ($p=0.0444$) and CTX/C225 ($p=0.0032$).

Median OS was measured from the time of randomization in the phase III EXTREME study but from the time of first treatment in the BNCT study. Time from randomization to treatment

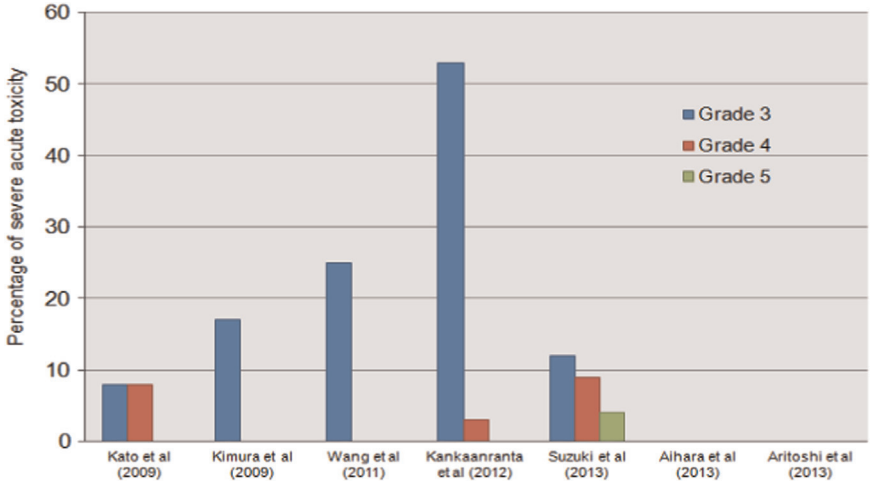

Fig. 1. Incidence (%) of reported severe acute adverse events (Grade 3–5) across BNCT trials.

Please cite this article as: Lim, D., et al., Clinical potential of boron neutron capture therapy for locally recurrent inoperable previously irradiated head and neck cancer. Appl. Radiat. Isotopes (2015), http://dx.doi.org/10.1016/j.apradiso.2015.07.044