Applied Radiation and Isotopes 88 (2014) 16–19

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

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

Case numbers for a randomized clinical trial of boron neutron capture therapy for Glioblastoma multiforme

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HIGHLIGHTS

- BNCT of Glioblastoma with BPA is not more effective than RT+TMZ.
- BNCT of Glioblastoma with BSH is probably more effective than RT+TMZ.
- A clinical trial with patients of class V and an unmethylated MGMT gene should be conducted.

ARTICLE INFO

Available online 4 December 2013

Keywords:
BNCT
BSH
BPA
Glioblastoma
Design of clinical trials

ABSTRACT

Boron neutron capture therapy (BNCT) with $Na_2B_{12}H_{11}SH$ (BSH) or p-dihydroxyborylphenylalanine (BPA), and with a combination of both, was compared to radiotherapy with temozolomide, and the number of patients required to show statistically significant differences between the treatments was calculated. Whereas arms using BPA require excessive number of patients in each arm, a two-armed clinical trial with BSH and radiotherapy plus temozolomide is feasible.

1. Introduction

Standard therapy for Glioblastoma multiforme (GBM) is surgery, followed by radiotherapy (RT) and concomitant temozolomide (TMZ; Stupp et al., 2005). Boron neutron capture therapy (BNCT) has long been advocated as an alternative to conventional treatment of GBM. BNCT requires the preferential accumulation of boron-containing compounds in the tumor. Two compounds, $Na_2B_{12}H_{11}SH$ (BSH) and p-dihydroxyborylphenylalanine (BPA), and recently also their combination, have been used for this.

Despite the fact that boron neutron capture therapy (BNCT) has been used clinically for the treatment of brain tumors (mostly GBM) for several decades (see, e.g., Joensuu et al. (2003) and Capala et al. (2003)), no reliable data have been published to date which show whether BNCT is equal or superior to standard therapy.

In this paper, we compare the data published for BNCT of GBM with BNCT (BSH or BPA, or a combination of BSH and BPA) with the standard therapy RT/TMZ, and estimate the numbers of patients who would have to be treated in a randomized clinical trial with the aim of showing the superiority (or inferiority) of BNCT to that of RT/TMZ. With such a clinical trial, the question of potential benefit of BNCT could possibly be answered.

2. Materials and methods

The data for survival of patients following RT/TMZ were taken from Stupp et al. (2005).

Data for BNCT were taken from the publications in Table 1. Only newly diagnosed cases were considered.

3. Analysis of data

Data were analyzed with the program SAS (SAS, Cary, NC, USA). Due to the very limited amount of data for BNCT treatments, Monte-Carlo simulations were carried out for sample size determination. These require the specification of survival functions. Different functions were fitted to the survival data available, and their quality was checked with the procedure PROC LIFER EG. We fitted exponential curves, Weibull distributions, Gamma

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http://dx.doi.org/10.1016/j.apradiso.2013.11.092

Table 1
Overview over data used in this paper.

# of patients	Study arm	RT 286	RT/TMZ 287	BPA[a] 29	BSH[b] 7	BPA+BSH[c] 10
Age	Median	57	56	53	51	–[d]
	Range	23–71	19–70	26–69	38–64	–
Sex # (%)	Male	171 (61)	185 (64)	16 (55)	2 (29)	–
	Female	111 (39)	102 (36)	13 (45)	5 (71)	–
WHO status # (%)	0	110 (38)	113 (39)	7 (24)	–	–
	1	141 (49)	136 (47)	19 (66)	–	–
	2	35 (12)	38 (13)	3 (10)	–	–
Resection # (%)	Biopsy	45 (16)	48 (17)	3 (10)	1 (14)	–
	Resection	241 (84)	239 (83)	26 (90)	6 (86)	–
Days from diagnosis to therapy (d)	Median	35[g,e]	35[g,e]	40	40	–
	Range	14–90[g]	12–75[g]	1–75	29–95	–
Median survival from diagnosis (mo)	Median	12.1	14.6	16[f]	23.3	14.1
	95% confidence interval	11.2–13.0	13.2–16.8	–	–	9.9–18.5

[a] Data taken from Henriksson et al. (2008).
[b] Data extracted from Yamamoto et al. (2009) for intraoperative treatment (protocol 1 of that paper).
[c] Data extracted from Kawabata et al. (2009, protocol 1).
[d] No data available.
[e] Days from randomization.
[f] Median survival from BNCT (mo).
[g] Converted from weeks to days for better comparison.

Table 2
List of most appropriate survival functions for the five study arms.

Arm	Functions
RT/TMZ	loglogistic
BPA	Gamma2, loglogistic
BSH	Weibull, loglogistic
BPA+BSH	Gamma3, loglogistic

distributions with two and three parameters (Gamma2 and Gamma3, respectively), logistic, and loglogistic distributions. The most adequate functions for the five study arms are listed in Table 2. The largest variations between the fits of different functions were found for the study arm BPA+BSH. The survival curves for all treatments, and the fits for RT+TMZ as well as BNCT with BSH, are found in Fig. 1.

With the functions, each of the two fits of each of the three BNCT arms was compared to each function fitted to RT or RT/TMZ. The determination of the sample size necessary to distinguish between the study arms was performed as follows.

A number of R samples (of equal sizes n for each of the two arms) were generated for the null hypothesis H_0 (the two treatments are not different) and alternative hypothesis H_1 (the two treatments are different). For each of the samples the statistics for median survival were calculated. The critical value t_{crit} for an α error of 0.05 was calculated for H_0, and this value was used to determine the power $(1-\beta)$ for H_1. These steps were repeated by increasing n until the power exceeded 0.8. Comparison between the different fits was done using the median survival time (MST). Other endpoints (e.g. log-rank) were not considered, due to the scarcity of data in the BNCT arms. Also, the RT+TMZ data appear to contain a subset of patients with considerably longer survival, which cannot be accounted for in the functions fitted.

4. Results

Slight differences between the different curves fitted to the published Kaplan–Meier plots were found. The differences were most prominent for the results of the loglogistic functions for BPA+BSH as compared to those with Gamma3. For the other treatments, the fitted curves were very similar, with the obvious exception of a purely exponential fit.

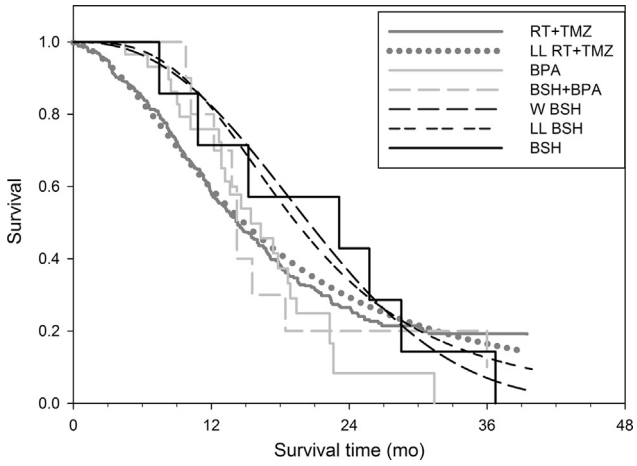

Fig. 1. Data for the treatment of GBM with radiotherapy+TMZ (dark gray solid curve) and the fit of a loglogistic function (dark gray dotted curve), with BPA (light gray solid curve), with BPA+BSH (light gray dashed curve), and with BSH (black solid curve). Shown are also fits of a Weibull function (W) and a loglogistic function (LL) to the BSH curve.

Table 3
Number of patients required in each of the study arms with median survival time and log rank as endpoints.

Arm1	Function	Median survival time (mo)	Arm2	Function	Median survival time (mo)	ΔMST (mo)	n
TMZ2	LL	15.32	BPA	G2	15.39	0.07	> 15,000
			BSH	W	20.47	5.15	62
			Mixed	G3	14.48	0.84	> 15,000
TMZ2	LL	15.32	BPA	LL	15.35	0.03	> 15,000
			BSH	LL	19.39	4.07	95
			Mixed	LL	15.63	0.32	> 15,000

Abbreviations of functions: LL=loglogistic; G2=Gamma2; G3=Gamma3.