The Phase I/II BNCT Trials at the Brookhaven medical research reactor: Critical considerations

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Abstract. A phase I/II clinical trial of boronophenylalanine-fructose (BPA-F) mediated boron neutron capture therapy (BNCT) for Glioblastoma Multiforme (GBM) was initiated at Brookhaven National Laboratory (BNL) in 1994. Many critical issues were considered during the design of the first of many sequential dose escalation protocols. These critical issues included patient selection criteria, boron delivery agent, dose limits to the normal brain, dose escalation schemes for both neutron exposure and boron dose, and fractionation. As the clinical protocols progressed and evaluation of the tolerance of the central nervous system (CNS) to BPA-mediated BNCT at the BMRR continued new specifications were adopted. Clinical data reflecting the progression of the protocols will be presented to illustrate the steps taken and the reasons behind their adoption.

1. INTRODUCTION

The first clinical trial of BNCT for patients with GBM was initiated at Brookhaven Graphite Research Reactor in 1951 [1]. From 1959 to 1961, a series of patients with intracranial tumors (all except one, primary malignant brain tumors) received BNCT at the Brookhaven Medical Research Reactor (BMRR). Another group of patients with malignant gliomas was treated at the reactor at the Massachusetts Institute of Technology (MIT) during 1959–1961. These trials used four different boron compounds and a variety of surgical interventions. Results from the BNL and MIT studies were disappointing and all clinical trials of BNCT in the United States were stopped. The disappointing results were attributed to 1) inadequate penetration of the thermal neutron beams and 2) poor localization of boron in the tumor: tumor-to-blood ^{10}B concentration ratios were less than 1 [1–4]. Efforts to deliver therapeutic neutron fluences to a tumor at considerable depth in the brain sometimes resulted in severe damage to the scalp. In retrospect, it is now considered that high boron concentrations in the blood contributed to the damage to the vascular endothelium [2, 4–6]. The late Hiroshi Hatanaka began clinical BNCT in Japan in 1968. Patients with malignant gliomas were treated using the boron delivery agent, sulfhydryl borane $Na_2B_{12}H_{11}SH$ (BSH) and thermal neutron irradiation with an open skull technique. One hundred and forty-nine patients were entered into this treatment program [7]. The median survival for the BNCT-treated group was slightly shorter than the median survival of "the group treated conventionally" [8]. An analysis of patients from the United States who received BNCT in Japan failed to show any significant advantage of BNCT over more conventional approach [9]. Hatanaka and Nakagawa have, however, observed several long term survivors in a subset of BNCT-treated patients [10]. Of 38 patients with grades 3 and 4 malignant gliomas treated between 1968 and 1985, the 5- and 10- year survival rates were 19.3% and 9.6%, respectively. Sixteen of these 38 patients had tumors within 6 cm of the cortical surface. The 5- and 10-year survival rates in this subset of patients were 58.3% and 29.2%, respectively. Such long term survival, even in a highly selected population, has not been observed following conventional therapies.

In the 1980's, improvements in neutron beams and boron compounds allowed BNCT to reemerge in the USA as a potentially useful method for preferential irradiation of tumor. A higher energy ("epithermal") neutron beam is now in place at the BMRR [11, 12]. The higher energy epithermal neutrons are moderated in tissue to become low energy thermal neutrons that can be captured more efficiently by ^{10}B nuclei. Theoretically, the epithermal neutron beam at the BMRR makes it possible to treat deeper supratentorial tumors with BNCT. At the present time there are two boron compounds that are reportedly useful for clinical BNCT, BSH and the amino acid analog *p*-boronphenylalanine (BPA). One of the rationales for the use of BSH in BNCT of intracranial malignancies is that it does not cross the normal blood brain barrier (BBB) [13]. Intracranial tumors are assumed to be devoid of a functioning BBB and expected to preferentially accumulate BSH. It has, however, been reported that the integrity of the BBB in primary and metastatic brain tumors is highly variable (14) which may explain some of the relatively low reported tumor:blood boron concentration ratios following administration of BSH [10, 15, 16]. Moreover, BBB-respecting agents such as BSH will concentrate in the perivascular zones of those regions of the brain, which normally lack a BBB. A uniform intravascular and extravascular boron distribution in tissues lacking a BBB would result in about a three-fold higher radiation dose to the endothelium in these regions from the $^{10}B(n,a)^{7}Li$ reaction than to endothelium in regions where the BBB is intact [5, 17]. The use of the more deeply penetrating epithermal neutrons at the BMRR would produce more neutron capture events at greater depths than would be possible with a thermal neutron beam. A boron carrier that preferentially accumulates in tumor cells independent of BBB function, such as BPA, would therefore, be a better match for epithermal neutrons. In preclinical BNCT studies in rats bearing 9L gliosarcoma, BPA was shown to be superior to BSH [18]. BPA is transported across the blood-brain barrier into the normal brain. The average concentration of boron in the normal brain is between 75% and 100% of that found in the blood, and the average macroscopic concentration of boron in the tumor is 2 to 4 times higher than that in the blood. A soluble complex of BPA and fructose, BPA-F [19] was infused intravenously at doses ranging from 100 to 170 BPA/kg in patients in conjunction with a debulking craniotomy. No adverse effects attributable to BPA-F were observed in these patients [20].

On September 13, 1994, the aforementioned advances in neutron beams and boron compounds led to the beginning of a test of the closed-skull BNCT for human GBM at BNL using BPA-F and epithermal neutrons under US-FDA IND #43,317. The primary objective of this protocol was to evaluate the safety of BPA-F mediated BNCT in patients with GBM. As a secondary objective, the palliation of GBM by BPA-F mediated BNCT would be assessed. Between Sept, 1994 and June 1999, 54 patients were treated with BPA-F based BNCT at the BMRR. These patients were treated on a variety of dose escalation protocols that test the tolerance of the CNS to this new type of binary therapy. In this report we discuss some of the issues considered in the preparation of the clinical trials as well as a historical perspective on how the trials progressed.

2. CRITICAL CONSIDERATIONS

The first of these issues deals with the tolerance of the normal tissues within the field, particularly the brain. The initial tolerances were established based upon data derived from both human and animal exposure to either single doses of photons [21–23] or single treatments with BNCT [24–25]. These studies suggested an upper limit for a safe dose to the whole brain of 10–11 Gy. Smaller volumes of brain, around 14 cm^3, were found tolerate doses of 20 Gy [26].

Glioblastoma multiforme was selected because of the exceedingly poor prognosis, less than 12 months median survival with standard therapy [27]. Maximum tumor depth was determined based on the limited thermal neutron flux to sites deeper than 6 cm. A Karnofsky Performance Status (KPS) of 70 or higher was chosen to minimize potential problems associated with the requirement that patients remain totally still during treatment, which lasts between 45 minutes and 2 hours. A KPS of 70 or higher also allows comparison with the Radiation Therapy Oncology Group (RTOG) database Recursive Partition Analysis (RPA) classes [27]. Patients with prior adjuvant therapies were excluded because of the unknown degree of increased susceptibility of normal brain to BNCT resulting from these treatments.

The decision to administer BNCT in a single fraction was based on the following reasons:

1. All human clinical BNCT data was based on single fraction treatments. The distribution of BPA, particularly to normal brain, following more than one fraction of BNCT is unknown.

2. Results of animal studies to date do not support the hypotheses that multiple fractions either protects normal brain or improve tumor control [28–29].

3. The tolerance of the central nervous system to single-fraction BNCT has not been reached and the possibility of a tumorcidal dose within these tolerance limits has not been explored.

The considerations that lead to the selection of BPA rather than BSH as the boron carrier were described in the introduction. To summarize BPA was found to actively accumulate in 9L gliosarcoma is nontoxic and crosses the blood brain barrier (18–20). As previously described the estimates of normal tissue radiation tolerance thresholds and the probable tumor control doses were based primarily on results of human and animal exposures to single dose of photons or single treatment with BNCT. There are many dose components in BNCT, each with a different relative biological effectiveness (RBE) [30]. The total effective BNCT dose is expressed as the arithmetic sum of RBE corrected absorbed doses of each component using the unit Gy-Eq (Gray-Equivalent). The estimated radiation tolerance thresholds for the average brain dose and maximum doses to basal ganglia, optic chiasm and scalp were 11, 11, 11, and 22 Gy-Eq, respectively. Pre-BNCT GBM debulking was required not only for tissue diagnosis and amelioration of any mass effect but also as a prophylactic measure to soften any single-fraction, high dose BNCT induced increase in intracranial pressure due to radiation-induced sterile tumor inflammation and/or necrosis and edema.

3. PROGRESSION OF THE DOSE ESCALATION IN THE CLINICAL TRIALS

3.1. Toxicity evaluation

The safety of BPA mediated BNCT was the primary objective of this study. CNS toxicity was evaluated based on post-BNCT follow-up reports. The patient information included history and physical examination, total and differential leukocyte counts, routine clinical tests of blood and urine, MRI brain scans, Mini Mental State scores, Karnofsky Performance Status scores, and acute and late BNCT mediated neurotoxicity scores. Grade 3 or grade 4 toxicity, if any, was to be scored as severe toxicity. Death directly related to BNCT was to be defined as grade 5 toxicity. The toxicity criteria and grading systems were based on the Cooperative Group Common Toxicity Criteria and Radiation Therapy Oncology Group

(RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) acute and late radiation morbidity criteria [31].

3.2. Dose escalation

For the first protocol in the dose escalation series a reference dose of 10.5 Gy–Eq was chosen. The reference dose was defined as the dose to a 1 cm^3 volume centered at the maximum of the thermal flux. The reference dose corresponded to the maximum dose, Dmax, when one field was used. Eleven patients were treated with a reference dose of 10.5 Gy-Eq. using an eight centimeter collimator at a reactor power of 2 megawatts (MW). During this time a pilot study, which included patients that did not fit the entry criteria of the first protocol, were given radiation using a reference dose of 12.6 Gy-Eq. No significant CNS side effects were documented in these 15 patients. Two autopsies were performed in this cohort. There was no evidence of histologic damage to the normal brain.

Encouraged by the results from the first 15 patients a new protocol was started with a prescribed reference dose of 12.6 Gy-Eq. The reference dose was then defined as the 1 cm^3 centered at the maximum of the thermal flux outside the tumor volume. The dose escalations were achieved by increasing the dose of BPA, the reactor operating power, the duration of irradiation, and by changing the neutron beam collimator. The increase in the collimator size also allowed for increased dose at depth. In this new protocol a stratifying criteria was established which separated the patients into two groups. Stratification occurred based on target volume. If the target could be treated to a minimum dose of 17 Gy-Eq with one field the patient will be placed on the single field group (protocol 4a). If the target was too big to be covered by the one field then the patient will be placed on the double field group (protocol 4b). A significant increase in the average brain dose was observed when two fields were used as seen in figure 1.

3.3. Increased incidence of side effects

As the dose escalation continued some non-CNS side effects were noted. These effects included, but were not limited to otitis, parotitis, and sinusitis. At this time new radiobiological studies in animals were commissioned to evaluate the boron concentration in other head and neck tissues as well as to test the radiobiological effectiveness of this therapy on skin, mucosae, and glandular tissues. These studies revealed that there was an increase concentration of boron in these head and neck tissues. Further evaluation indicated that the radiobiological effectiveness of BNCT with BPA in the mucosae is higher than previously expected. As new information was uncovered the dose evaluation for treatment planning was revised accordingly.

In protocol 4 there were three acute RTOG grade 3 CNS toxicity documented. These responded rapidly to intravenous decadron infusion. The lesson learned from these three cases was the importance of maintaining a high level of decadron prior to and immediately after the BNCT treatment to avoid pre-treatment brain edema. Eight patients in this group had seizures. All of them had subtherapeutic levels of antiseizure medication during and/or after the procedure. Another lesson learned here was to maintain the level of antiseizure medication therapeutic during and after the treatment. Since we established these policies of premedicating the patients, with therapeutic levels of antiseizure medications and high dose steroids, no seizure or acute grade 3 CNS toxicity has been documented. Results from 10

autopsies in this cohort, with a maximum average brain dose (ABD) of 6 Gy-Eq, revealed that at these doses there was no significant radiation damage to the CNS.

3.4. Tumor response

As the ABD was escalated (Fig 1), the dose to the tumor increased (Fig 2). The time to progression (TTP) from diagnosis did not change significantly from protocol to protocol. The median TTP has not shown any dose response (Fig 3). Survival is not an adequate endpoint since it is dependent on the aggressiveness of the post progression treatment and not on the actual BNCT dose. One parameter that has not seen a perceptible change throughout the protocols is the average blood boron concentration (ABBC) (Fig 4). It is essential to increase the boron concentration in the blood and subsequently in the tumor to take full advantage of this binary therapy.

Salient characteristics of the first five protocols are shown in Table 1. Table 2 summarizes the parameters modified as the doses were escalated.

TABLE I. BNCT clinical trial summary

Protocol	Comments	Number of patients	Reference Dose (Gy-Eq)	Ave. Brain Dose (Gy-Eq)	Min. Tumor Dose (Gy-Eq)	Min. Target Dose (Gy-Eq)
1	9/94	1	10.5	(2.3)	(27)	(16)
2	2/95	10	10.5	<7.5	>20	not specified
3	Pilot study:	4	12.6	<7.5	>20	not specified
4a	1-field 6/96	11	12.6*	<7.5	~30	~17
4b	2- fields 6/96	17	12.6*	<7.5	~30	~17
5	3-fields 10/98	7	15*	<11	>30	~29**

*Reference outside tumor
**Redefined target

TABLE II. BNCT dose escalation parameters

BPA	250 mg/kg, 290 mg/kg or 330 mg/kg
Reactor Power	2 MW or 3MW
Collimators	8 cm or 12 cm
Treatment Fields	Single, Double or Triple
Treatment Time	38 min to 120 min
Reference Brain Dose	10.5 Gy-Eq or 12.6 Gy-Eq

4. CURRENT PROTOCOLS

Based on the low toxicity seen up to protocol 4, several protocols were designed. Protocol 5 is a continuation of the dose escalation of single fraction BNCT with reference dose of 15 Gy-Eq and escalating ABD up to 11 Gy-Eq. The required minimum target volume dose was 29 Gy-Eq for this protocol. Protocol 6 is two fraction BNCT for patients who do not qualify for protocol 5. This protocol was designed to answer the question of possible advantages of boron redistribution in tumor and potential changes in the tolerance of normal tissues after fractionation. Protocol 7 used double fraction BNCT to treat patients with tumor volumes ≤ 50 cm^3 who had minimally invasive diagnostic biopsy only. This was designed to evaluate possible changes in the CNS side effect profile when treating intact tumors. Protocol 8 used single fraction BNCT to treat patients with recurrent debulked GBM after a single course of radiation. Out of eleven patients accrued in these 4 protocols 7 have been placed in protocol 5, 2 in protocol 6 and one each in protocol 7 and 8.

For the current protocols the target volume definition was changed from the gadolinium enhanced region plus a 2 cm shell around it, to the larger of the postoperative gadolinium enhanced region or the preoperative peritumoral edema and the 2 cm shell that encompasses it. This change reflected our observation that all recurrences occurred locally and their progression followed the preoperative edema volume pattern and data from Kelly et. al.[32]. The initial target volume definition used in the RTOG malignant glioma protocols RTOG-9305 and 9411 was adopted. This included the volume of edema in the target, where the risk for recurrence is highest. It also made the volumes used to report our data consistent with the volumes used in the radiooncologic literature. It is too early to tell what the long term effects in patients accrued under the current protocols will be.

5. CONCLUSIONS

Based on the results from the first 4 dose escalation protocols and 12 autopsies we can conclude that BNCT at doses of up to 6 Gy-Eq using BPA-F at the BMRR is safe. In this group of 43 patients there appears to be no improvement in tumor response as dose escalates, when using TTP as an endpoint. The BPA-F dose has been marginally escalated so far and more aggressive escalation of the boron dose is indicated to improve tumor response. BNCT boron dose optimization trials should continue.

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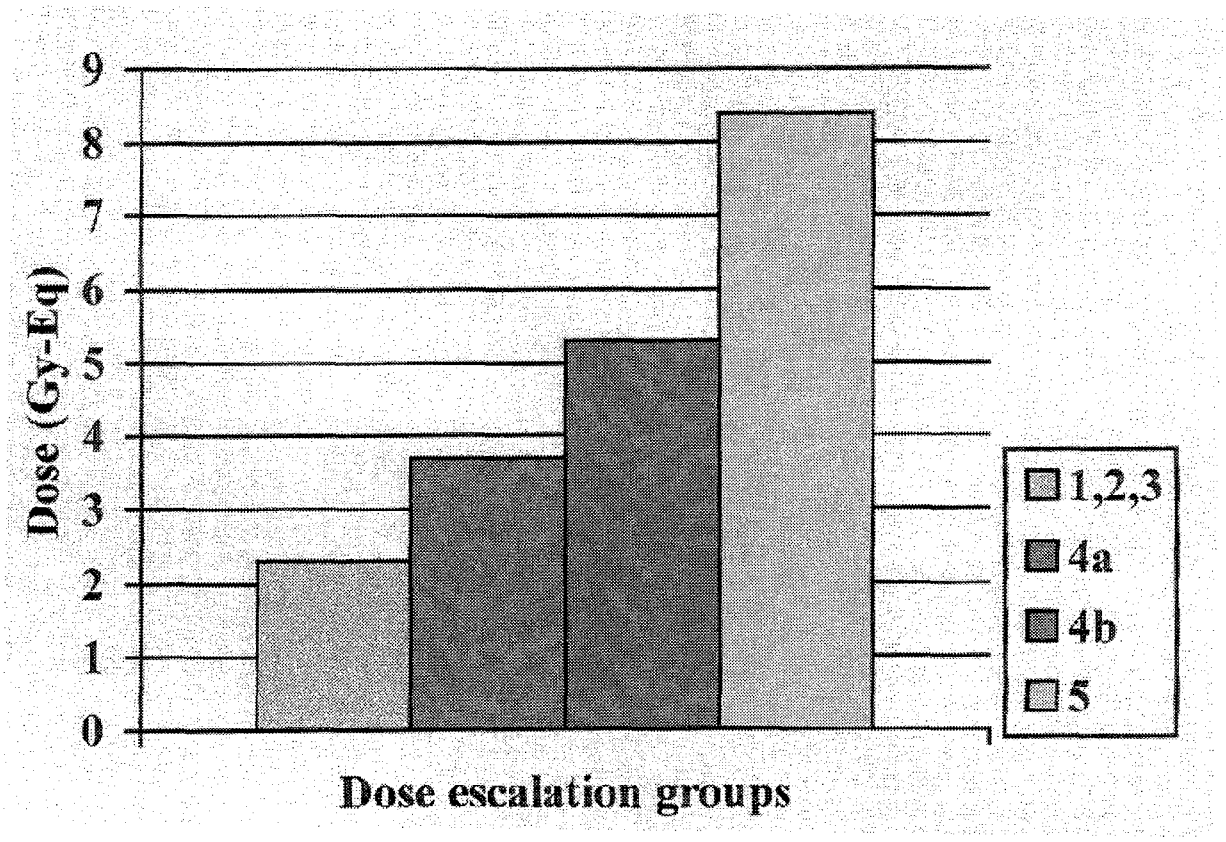

FIG. 1. Average Brain Dose escalation by protocol.

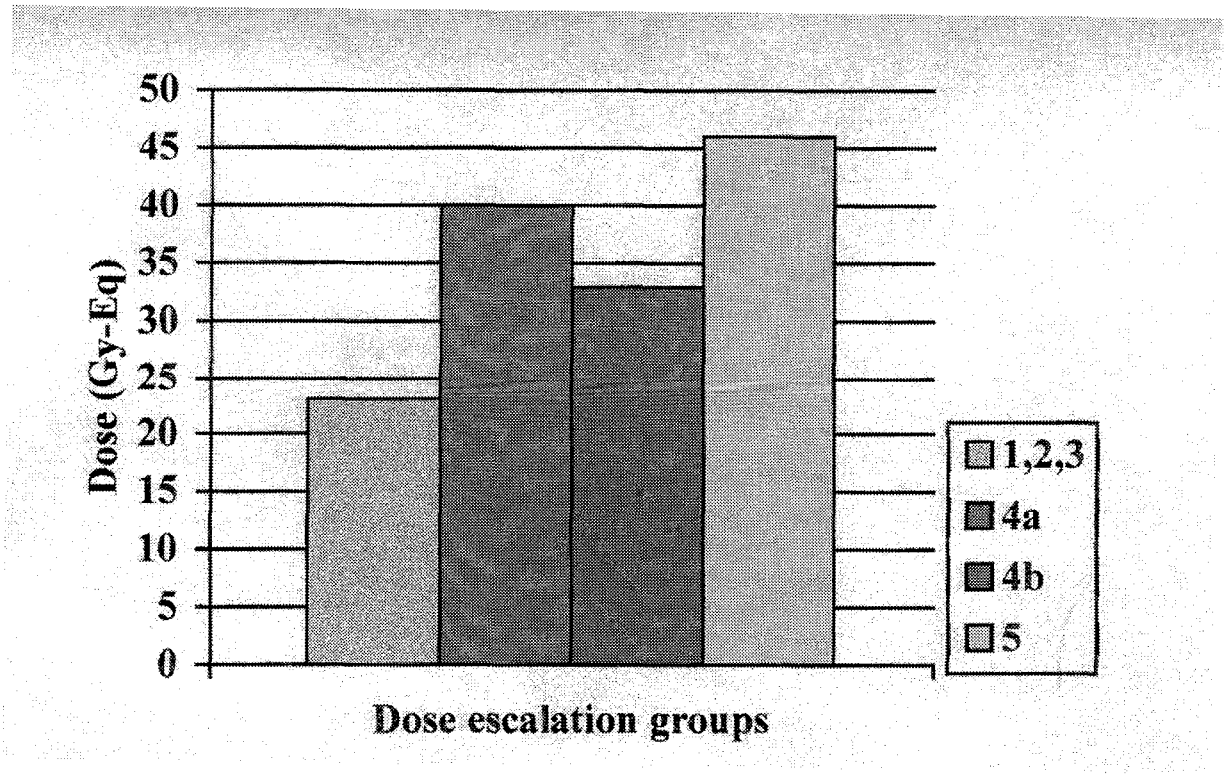

FIG. 2. Minimum Tumor Dose escalation by protocol.

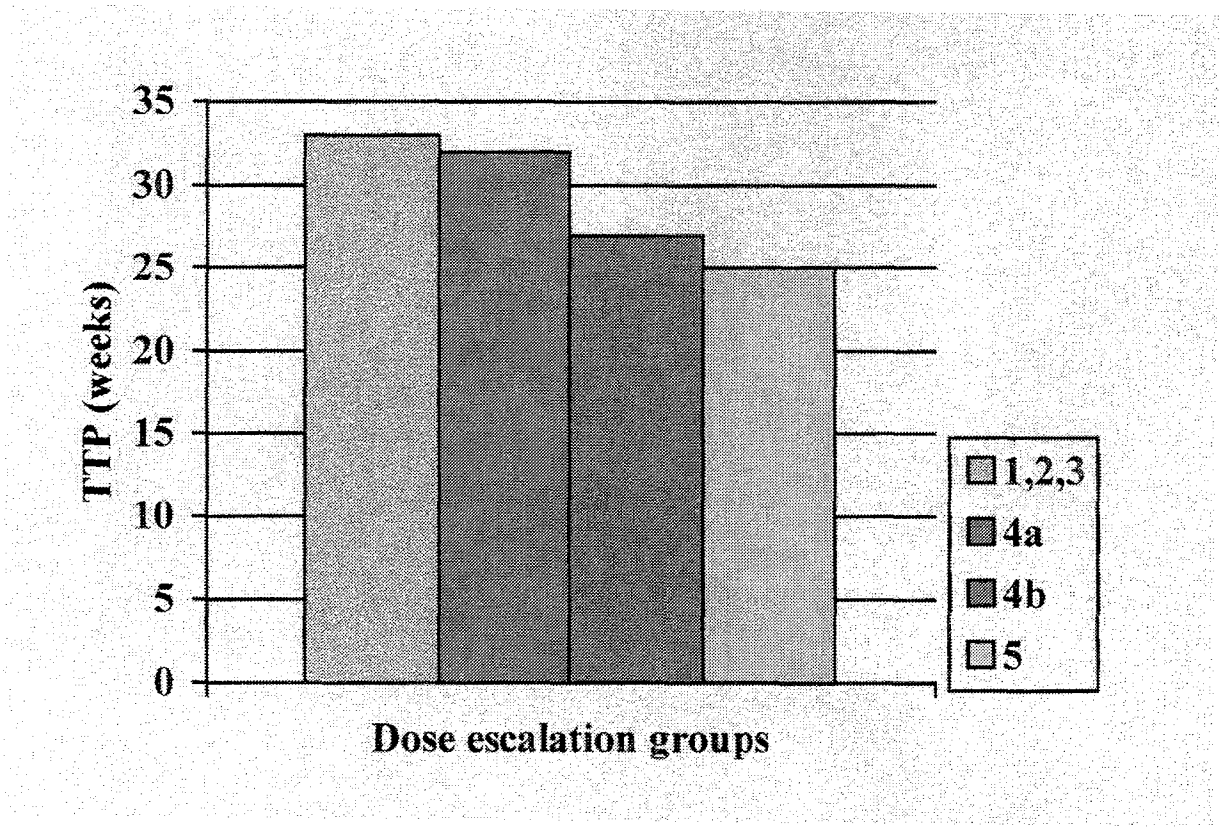

FIG. 3. Time to Progression (weeks) by protocol.

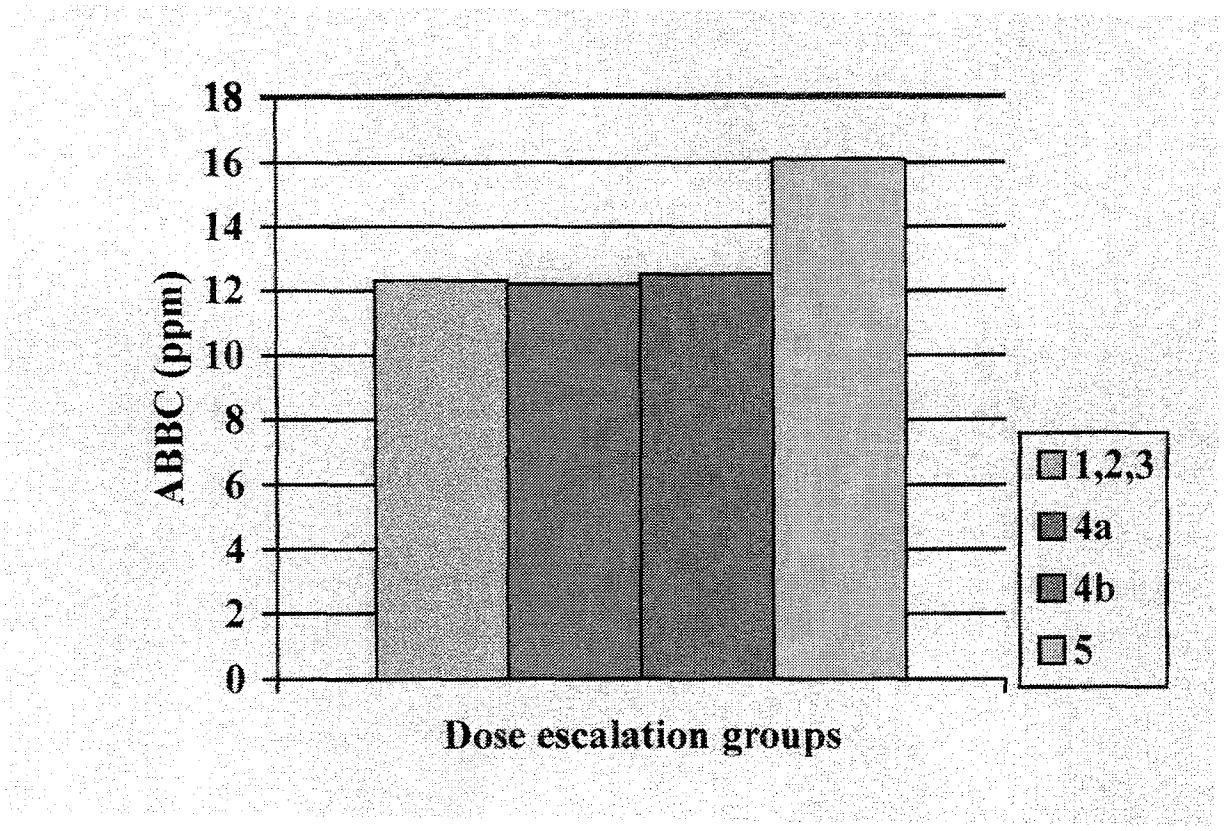

FIG. 4. Average Blood Boron Concentration (ppm) by protocol.

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