

Novel Pharmacological and Magnetic Resonance Strategies to Enhance Boron Neutron Capture Therapy (BNCT) Efficacy in the Clinical Treatment of Malignant Glioma

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1. Introduction

High-grade glioma, such as anaplastic astrocytomas (AA, WHO grade 3) and glioblastomas multiforme (GBM, WHO grade 4) are extremely aggressive and highly infiltrative brain tumours (Kleihues & Cavenee, 2000; Louis et al., 2007). In most cases they recur locally after applying the standard multimodality treatment based on surgical resection, followed by radiotherapy and/or chemotherapy. Despite advances in medicine, malignant gliomas continue to carry a dismal prognosis, even though a modest increase (by 4.5 months) in median survival and quality of life has been achieved. The main limitation to the effectiveness of surgery and radiotherapy in patients suffering from high-grade glioma is that these techniques, based on the geometric definition of tumour volume, are not suitable to eradicate tumour infiltrating cells within normal brain tissue. Moreover adjuvant chemotherapy has little effect on prolonging survival in patients with GBM (Stupp et al., 2005). As a consequence, novel therapeutic approaches, based on a better understanding of cancer biology, are needed. To this end, experimental therapies such as gene therapy (Mischel et al., 2003), antiangiogenic therapy (Van Meir et al., 2010), monoclonal antibodies (Zhu et al. 2010), cancer immunotherapy (Keunen et al., 2011), vaccines (Hickey et al., 2010), boron neutron capture therapy (BNCT) (Barth et al., 1992, 2005) and radioimmunotherapy (Joensuu, 2000) are under investigation. Among these, BNCT represents a promising adjuvant therapy for malignant glioma, and for other forms of cancer such as head/neck cancer. It is a binary form of radiation therapy based on the selective accumulation of boronated compounds within tumour cells which are then irradiated by low-energy thermal neutrons. The nuclear reaction that occurs between the stable isotope, ^{10}B , and thermal neutrons, yields high-energy alpha particles and recoiling lithium nuclei which release most of their ionizing energy within a few microns (about one cell diameter), therefore limiting radiation damage only to ^{10}B -containing cells. Thus, BNCT can be considered as a biologically targeted form of radiation therapy because of its ability to target tumour cells

through boron compounds which selectively accumulate within them. Given this selectivity of BNCT, infiltrating tumour cells, as well as subclinical lesions, can be targeted by ^{10}B compounds and underwent the therapeutic effect.

For effective BNCT a large amount of ^{10}B nuclei (about 10^9 atoms of ^{10}B per cell) (Barth & Soloway, 1997) should be selectively accumulated within tumour cells, whilst ^{10}B concentration levels in blood and in normal brain tissues should be the lowest. At the same time, a tumour-to-brain (T:Br) ^{10}B concentration ratio of at least 3:1 must be achieved to ensure the optimal therapeutic dose to the tumour. Furthermore a sufficient number of thermal neutrons (thermal neutron fluences should be greater than 10^{12} n-cm $^{-2}$) must be captured by ^{10}B atoms into the target volume during irradiation (Barth & Soloway, 1997).

BNCT therapy has been evaluated for safety and efficacy in several centres around the world. So far, no severe effects of BNCT-related toxicity have been observed (Phase I), whilst little evidence of therapeutic effectiveness has been evaluated (Phase II) in patients with GBM (Diaz, 2003). Presently the therapy is under experimentation in Phase II clinical trials, while a randomized Phase III study has not yet been justified because of previous disappointing results.

Currently, the boron carrier most widely used for clinical purpose is the boronated derivative of the essential amino acid L-phenylalanine, *p*-boronophenylalanine (BPA). Due to its poor solubility at physiological pH, it is administrated as a complex with fructose (BPA-fr complex). It is widely accepted that BPA is actively transported across the blood brain barrier (BBB) into the normal glia, while its uptake within the tumour is due to an increased rate of L-amino acid transport across the tumour cell membrane (Wittig et al., 2000). In addition, BPA accumulation within tumour cells increases during the cell cycle (S-phase) so that its use in treating aggressive GBM might be an advantage. Furthermore it has been demonstrated that pre-treatment with L-tyrosine (Papasprou et al. 1994), or other molecules targeted by L or A amino acid transport systems, can enhance intracellular BPA accumulation (Wittig et al., 2000). Previous *in vitro* (Wittig et al., 2000) and *in vivo* (Capuani et al., 2008, 2009) studies have demonstrated that preloading with L-DOPA (a well-known molecule with chemical structure similar to those of L-tyrosine and BPA) improves the accumulation of BPA. As a consequence, more interest is being devoted to the potential clinical application of L-DOPA preloading. Indeed, due to the wide clinical experience with the administration of L-DOPA for the treatment of Parkinson's disease, its use as a potential enhancer of BPA accumulation in BNCT clinical trials could be immediately applied.

The main limitations for BNCT effectiveness are due to: a) insufficient ^{10}B intake within tumour cells, even if the most efficient methods of ^{10}B administration are utilised; b) the lack of reliable imaging methods for monitoring the bio-distribution of ^{10}B -carriers in order to estimate both the effectiveness of the carrier and the optimal timing for neutron irradiation (that is when T:Br ^{10}B concentration ratio achieves the maximum value whilst at the same time the ^{10}B concentration in blood is the lowest).

Our research work has focused on developing solutions to overcome these BNCT limitations, in order to make it a clinically useful treatment modality in the near future. Specifically, we have evaluated *in vivo* (using C6 glioma model) the pharmacokinetics of BPA, and the effect of L-DOPA preloading on BPA accumulation both in the tumour and normal tissues. Pharmacokinetic data were helpful in determining the optimal irradiation time, as well as to develop computational strategies in order to define as accurately as possible the radiation dose released within tumour and surrounding healthy tissues.

In order to determine the best fitting curve of BPA pharmacokinetics (used to extrapolate the BPA concentration over time after infusion), *in vivo* monitoring of ^{10}B -carrier was performed using nuclear magnetic resonance (NMR), either by imaging (MRI) or by spectroscopy (MRS). In both cases, the fluorinated analogue of BPA, F-labelled BPA, was investigated using ^{19}F -MRI and ^{19}F -MRS (Porcari et al., 2006, 2008, 2009). All previously mentioned methodologies and strategies designed to overcome some fundamental limitations of BNCT therapy have been developed to ensure a straightforward transfer from pre-clinical to clinical applications.

2. Principles of boron neutron capture therapy

BNCT is an experimental, radio-therapeutic modality able to biologically target malignant cells. It theoretically allows a *selective* delivery of the radiation damage within an infiltrating cancer cell while preserving the surrounding healthy tissues.

BNCT has been preferentially employed in clinical trials designed for the treatment of GBM (Henriksson et al., 2008; Yamamoto et al., 2008, 2011; van Rij et al., 2005). This high grade tumour of the central nervous system is highly malignant and extremely infiltrative, characterized by rapid tumour growth with a wide microscopic invasion of malignant cells within the normal parenchyma. It is extremely resistant to all current therapies, including surgery, chemotherapy, radiotherapy, immunotherapy and gene therapy. Despite advances in medicine, its prognosis is still very poor with a median survival time of less than one year (Ohgaki & Kleihues, 2005). Thus, GBM remains one of the challenges to be faced by physicians and scientists worldwide. BNCT holds therapeutic promise for these incurable tumours. Clinical interest in BNCT has also been focused on high-grade gliomas (Chanana et al., 1999), as well as the treatment of malignant meningiomas (Tamura et al., 2006) and cutaneous melanomas (Mishima & Kondoh, 2000). More recently, interest has been extended to other forms of neoplasms such as head-neck cancers (Kankaanranta et al., 2007), liver (Wittig et al., 2008a) and lung tumours (Suzuki et al., 2007), as well as undifferentiated thyroid cancers (Dagrosa et al., 2007).

The treatment is binary and is carried out following two distinct phases. Firstly, an intravenous infusion of ^{10}B -enriched compounds is given to the patient, allowing the selective uptake of ^{10}B -carriers within neoplastic cells. Subsequently, when the T:Br ^{10}B concentration ratio has achieved its highest value (at least 3:1) and, at the same time, the ^{10}B concentration in blood is the lowest, the patient is irradiated with low energy ($E < 0.4\text{eV}$, thermal) or higher energy ($0.4\text{eV} \leq E \leq 10\text{keV}$, epithermal) neutrons.

BNCT is based on the nuclear reaction $^{10}\text{B}(\text{n},\alpha)^7\text{Li}$ (1) (Sauerwein, 1993) that occurs when the stable isotope, ^{10}B (characterized by a high thermal neutron capture cross section) captures a thermal neutron (n_{th}) to yield $^{11}\text{B}^*$ in an unstable form, which decays in highly cytotoxic alpha (^4He) and lithium (^7Li) particles (Fig. 1.a). Due to their high Linear Energy Transfer (LET) (ICRU, 1998), these heavy charged particles release along their paths (comparable with the cell diameter, 5-9 μm) a great density of ionization responsible for elevated Relative Biological Effectiveness (RBE) (ICRU, 1998). Thus, the dose delivered and the radiation damage is mostly confined within the ^{10}B -loaded tumour cell (Fig. 1.b).

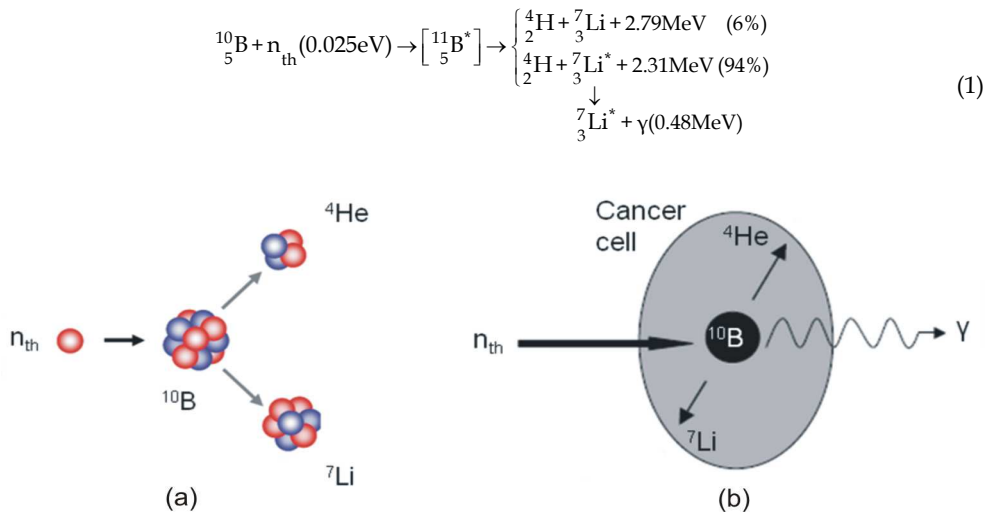


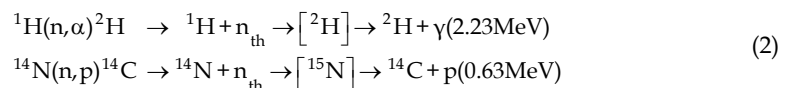
Fig. 1. ${}^{10}\text{B}(\text{n},\alpha){}^7\text{Li}$ reaction (a); cellular damage of BNCT (b).

The effectiveness of the therapy is dependent on two conditions:

- a high number of ${}^{10}\text{B}$ atoms must be selectively localized within neoplastic cells (at least 20-35 $\mu\text{g/g}$ $\sim 10^9$ atoms of ${}^{10}\text{B}$ per targeted cell) (Barth et al., 1996; Barth & Soloway, 1997);
- a sufficient number of thermal neutrons has to reach and be captured by the ${}^{10}\text{B}$ atoms into the target volume during irradiation (thermal neutron fluences should be greater than $10^{12} \text{ n cm}^{-2}$) (Barth et al., 1996; Barth & Soloway, 1997).

Although theoretically only a few alpha particles, releasing their energy within a cancer cell, assure the cell death, both of the above conditions should be satisfied because of the low probability of interaction between a single ${}^{10}\text{B}$ atom with a thermal neutron.

The therapeutic gain of BNCT is strictly dependent on the achievable T:Br ${}^{10}\text{B}$ concentration ratio between tumour and normal tissue. It has been established that the higher the T:Br ${}^{10}\text{B}$ concentration ratio is, the better the therapeutic gain of BNCT. Moreover, the tolerance dose of normal tissues should not be exceeded. It is mainly dependent on the neutron capture reactions, ${}^1\text{H}(\text{n},\gamma){}^2\text{H}$ and ${}^{14}\text{N}(\text{n},\text{p}){}^{14}\text{C}$ (2) (Soloway et al., 1997), that occur when hydrogen, ${}^1\text{H}$, and nitrogen, ${}^{14}\text{N}$, isotopes (with relative abundances of 3% and 10%, respectively, in normal tissue) capture thermal neutrons yielding low LET γ rays and high LET protons (2), respectively.



Due to the small neutron capture cross-sections of ${}^1\text{H}$ and ${}^{14}\text{N}$ ($\sigma_{\text{H}} = 0.332$ and $\sigma_{\text{N}} = 1.82$ barns; 1 barn = 10^{-24} cm^2) compared with that of ${}^{10}\text{B}$ ($\sigma_{\text{B}} = 3838$ barns), the dose released within surrounding healthy tissues is, in most of cases, much smaller than that delivered within the tumour, even though its value is dependent on neutron fluences. Thus, the upper limit of the neutron fluences is determined by the normal tissue tolerance dose for protons

and γ rays. As a consequence, for the best therapeutic result the T:Br ^{10}B concentration ratio should be as high as possible.

In order to satisfy the previous conditions, intensive investigations have been performed since the introduction of BNCT in most of the research centres worldwide. Considerable efforts have been directed towards the design and synthesis of new efficient boron agents, as well as in developing strategies to maximize the tumour boron uptake whilst minimizing, at the same time, ^{10}B levels in blood and in normal brain. The disappointing outcomes of early BNCT clinical trials in the United States (Slatkin, 1991) were mainly due to the inability of thermal neutrons to deliver therapeutic neutron fluences to deep-sited brain tumours. To overcome this, the use of higher energy epithermal neutron beams was pursued because of their greater tissue penetrating properties. Indeed, when epithermal neutrons penetrate tissues, they are slowed down into the thermal neutron range (Seppälä et al., 2002, Coderre et al., 1997) by means of collisions with atoms (Fig. 2). Epithermal neutrons, therefore, allow delivery of therapeutic fluences of thermal neutrons at greater depths in the brain without reflecting the scalp or doing a craniotomy as required by using thermal fluences.

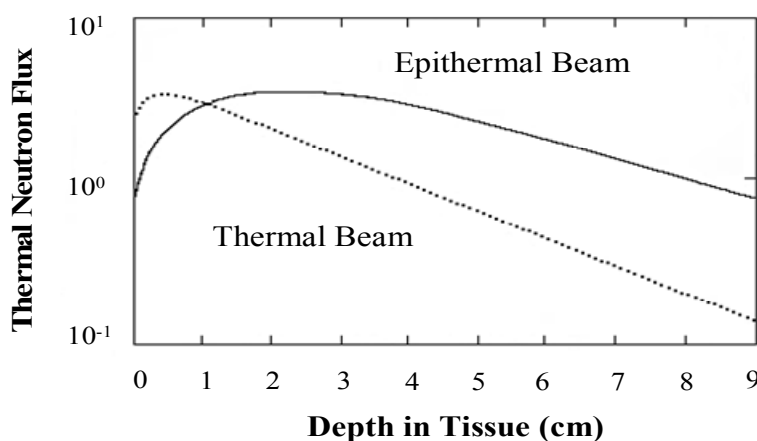


Fig. 2. Variation of the thermal neutron fluence with tissue depth using a thermal or epithermal neutron beam (Coderre & Morris, 1999).

Currently, nuclear reactors are the only sources of neutrons for clinical BNCT. The neutrons are produced by the fission process in the core of the reactor and are classified according to their energy as thermal ($E_{\text{th}} < 0.025\text{eV}$), epithermal ($0.4\text{eV} < E_{\text{epi}} < 10\text{keV}$) or fast ($E_{\text{fast}} > 10\text{keV}$). Since it is highly unlikely that the reactors can be sited in the main medical centres, alternative sources of thermal and epithermal neutrons for BNCT are being sought (Blue & Yanch, 2003). Among these, low-energy proton accelerators with low z targets are the most attractive.

At present several reactors creating optimal epithermal neutron beams for BNCT are being used clinically worldwide. They include the Massachusetts Institute of Technology Reactor (MITR) (Busse et al., 2003) in the USA, the Kyoto University Research Reactor (KURR) and JRR4 at the Japan Atomic Energy Research Institute (Nakagawa, 2003) in Japan, and the RA-6 CNEA reactor in Bariloche (Riley et al., 2008), Argentina. In Europe there are several clinical BNCT nuclear reactors: the FiR1 clinical reactor in Helsinki (Finland) (Joensuu et al.,

2003), the LVR-15 reactor at the Nuclear Research Institute in Rez (Czech Republic) (Burian et al., 2004) and the clinical reactor at Studsvik Medical AB (Sweden) (Capala et al., 2003).

2.1 Boron agents

Since its inception, the development of boron delivery agents for BNCT therapy has been one of the most important topics to fulfil. For BNCT to be successful ^{10}B carriers should satisfy the following requirements:

- selectivity for malignant cells (with preferential ^{10}B intracellular localization) compared with blood and contiguous normal tissue;
- achievement of tumour boron concentrations of at least $20\text{--}35\ \mu\text{g}^{10}\text{B}/\text{g}$ (approximately 10^9 boron atoms per cell);
- permanence (at a constant concentration) within tumour during the BNCT radiation procedure and rapid clearance from both blood and normal tissues. This is necessary to estimate the radiation dose delivered to tumour, brain and vascular endothelium;
- minimal systemic toxicity in order to achieve adequate tumour concentrations *in vivo* assuring, at the same time, favourable T:Br and tumour-to-blood (T:Bl) concentration ratios (at least 3:1);

So far, two ^{10}B carriers have been used clinically: the polyhedral borane, sodium borocaptate ($\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$ or BSH) (Fig. 3), and the dihydroxyboryl derivate of phenylalanine, boronophenylalanine ($\text{C}_9\text{H}_{12}\text{BNO}_4$ or BPA) (Fig. 3).

Both compounds are characterized by low toxicities, selective tumour cell uptake, long tumour persistence and safety after their intravenous (i.v.) administration.

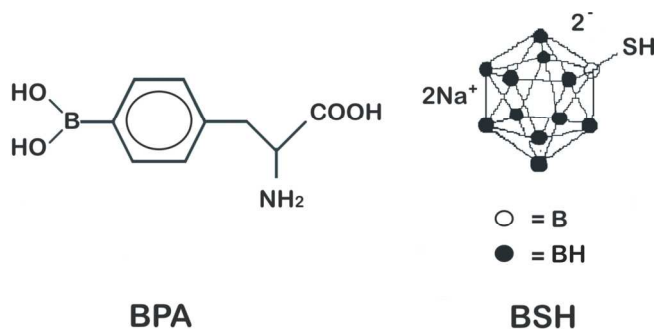


Fig. 3. Chemical structures of BPA and BSH.

Moreover, it has been demonstrated that either BPA or BSH may be able to target both proliferating and non-proliferating cells. This is of major importance for GBM treatment because of the relatively small percentage of GBM cells in the proliferative status at any time. Previously, BPA and BSH have been employed as boron agents in clinical trials designed for brain tumour treatments in the United States of America (Chanana et al., 1999; Coderre et al., 1999), in Europe (Phase I) (Capala et al., 2003; Joensuu et al., 2003; Burian et al., 1994) and in Japan (Phase II) (Nakagawa et al., 2003). The results of these trials confirmed the therapeutic efficacy of BNCT and provided the basis of the subsequent experimental clinical trials. However, the design of BNCT clinical protocols carried out using both mentioned ^{10}B -carriers was also influenced by the findings on animal model studies (Nakagawa et al., 2007; Smith et al., 1996).

In recent years, the clinical use of BPA for the GBM treatment has aroused great interest (Coderre et al., 1997; Capala et al., 2003; Joensuu et al., 2003) because of its encouraging results in experimental brain tumour therapy. Due to its low solubility in aqueous solutions at physiological conditions (pH ~ 7.4) it is administered as a complex with fructose (BPA-fr complex) (Yoshino et al., 1989). It was observed that BPA can be selectively accumulated either in the main tumour mass or in the microscopic cluster of tumour cell invading the normal parenchyma, even though the measured ^{10}B concentration in the isolated cluster was only about 50% of that obtained in the main tumour mass (Smith et al., 1996). This result is of great importance for the efficacy of BNCT because the isolated clusters represent potential sites of tumour re-growth. Furthermore the ability of BPA to target the microscopic cluster within the normal brain suggests that it is actively transported through the BBB.

Although the details of BPA accumulation into tumour cells are not completely understood, it is accepted that it is due to an elevated rate of amino acid transport across the tumour cell membrane (Wittig et al., 2000). Furthermore, there is evidence that BPA accumulation is enhanced by a pre-treatment with molecules vehiculated through L or A amino acid transport systems (Wittig et al., 2000). The increase of BPA intracellular accumulation was also demonstrated in mouse melanoma cells (Papasparyou et al., 1994) using L-tyrosine pre-administration.

In addition, it has also been demonstrated that BPA accumulation within tumour cells increases during the cell cycle (S phase) (Nichols et al., 2002) so that its use in the treatment of aggressive brain gliomas might be an advantage.

3. Main limitations for BNCT effectiveness

BNCT is one of the most complex therapeutic modalities used to treat malignant brain tumours. Its success or failure is highly dependent on a combination of several chemical, physical and biological factors. Up to now, BNCT has been trialled to investigate its safety and efficacy in several centres worldwide. However, to date, the results of Phase I and II clinical trials have not shown therapeutic responses to justify Phase III trials.

These disappointing results are mainly due to the following limitations.

The first limitation was mostly due to insufficient uptake of ^{10}B -labelled compound within tumour cells even though the most advanced methods of ^{10}B administration were used (Chanana et al., 1999; Elowitz et al., 1998).

Normally, the ^{10}B uptake within brain tumours may be influenced by several factors such as the BBB permeability to the ^{10}B -carrier, the plasma concentration profile of the ^{10}B -agent (which is dependent on either the drug dose or the way of administration), the blood flow within tumour as well as the drug lipophilicity.

So far, some strategies have been proposed to improve BNCT effectiveness by increasing BPA and BSH tumour intake. Some of these, including the use of pharmacological agents such as mannitol (Barth et al., 2000) or Cereport (RMP-7) (Yang et al., 1997) to disrupt the BBB, have been experimented on animal models (Barth et al., 2000; Yang et al., 1997). Although the results showed an increase in T:Br and T:Bl indices, the potential toxicities were not completely investigated. Moreover these methodologies have been classified as invasive, so numerous investigations are needed before considering them as potential applications in future clinical trials.

The second main limitation for BNCT effectiveness was due to the lack of efficient imaging methods to monitor the spatial bio-distribution of ^{10}B -labelled compounds and their

pharmacokinetics, in order to estimate the efficacy of the carrier and the optimal timing of neutron irradiation. This ideal time is when the ^{10}B concentration in tumour is higher than the concentration in blood and surrounding healthy tissues to prevent damage to these regions. Previous studies carried out in order to estimate brain-to-blood (Br:Bl), T:Br and T:Bl ^{10}B concentration ratios using kinetic models (Ryyanen et al., 2000; 2002) and Inductively Coupled Plasma-Atomic Emission Spectrometry (ICP-AES) (Laakso et al., 2001) techniques, gave different results.

Up to now several techniques (Wittig et al., 2008b) have been used to determine the spatial distribution and pharmacokinetics of ^{10}B agents (Elowitz et al., 1998; Ryyanen et al. 2000, 2002, Laakso et al., 2001, Kabalka et al., 2003, Wang et al., 2004). Among these, MRI and MRS provide useful methods for non-invasive and non-destructive real-time monitoring of ^{10}B compounds during BNCT treatment *in vivo*. Given the low sensitivity of the ^{10}B NMR method (Bendel et al., 2001; Bendel 2005) and the intense proton background signal that makes ^1H -MRS (Zuo et al., 1999) and Magnetic Resonance Spectroscopy Imaging (MRSI) (Bendel et al., 2005) techniques problematic *in vivo*, new strategies to detect BPA by NMR are in progress.

4. Strategies to improve the efficacy of the therapy

In order to make BNCT a clinical useful treatment modality in the near future, our work aims at investigating solutions to overcome the main limitations to the efficacy of the current methodology.

Firstly, with the aim of improving the effectiveness of the therapy by increasing BPA tumour intake, the strategy used was to assess the effect of L-DOPA pre-loading on BPA accumulation within the tumour.

L-DOPA is a well-known molecule with a chemical structure similar to those of L-tyrosine and BPA. Its use as a potential enhancer of BPA accumulation was suggested by previous encouraging results obtained on both mouse melanoma (Papasprou et al., 1994) and 9L rat gliosarcoma cells by pre-administration of L-tyrosine (Wittig et al., 2000). The enhancement of BPA accumulation in 9L rat gliosarcoma cells has been also replicated by using pre-treatment with both molecules targeted by L and A aminoacid transport system. These findings suggest that the substrate-coupled antiport (exchange) mechanism of these transporters is enhanced by the preloading of specific aminoacids. Previous *in vitro* (Wittig et al., 2000) and *in vivo* (Capuani et al., 2008; 2009) studies have demonstrated that L-DOPA preloading improves the accumulation of BPA in the tumour. Specifically it was demonstrated *in vivo* (Capuani et al., 2008; 2009) that L-DOPA pre-administration on C6 glioma model gave rise to an increase of BPA tumour accumulation of 2.7 times with respect to those of controls. Conversely, no significant difference was evaluated by using the High Performance Liquid Chromatography (HPLC) method in both blood and normal brain between L-DOPA preloaded rats and controls. These findings are of fundamental importance for their impact on potential clinical applications. Indeed, the introduction of L-DOPA as a potential enhancer of BPA accumulation in BNCT clinical trials could be of immediate application because of its established clinical use as a treatment for Parkinson's disease.

Then, with the aim of investigating the pharmacokinetic behaviour of ^{10}B carriers and their boron bio-distribution, both of them essential to evaluate the efficiency of the carrier and the optimal irradiation time, a novel approach to detect BPA was proposed. The strategy used was to map the fluorinated analogue of BPA (^{19}F -BPA-fr complex) (Fig. 4) using ^{19}F NMR in a way

similar to Positron Emission Tomography (PET) studies (Kabalka et al., 2003; Wang et al., 2004). The feasibility of the method was previously demonstrated *in vitro* (Porcari et al., 2006).

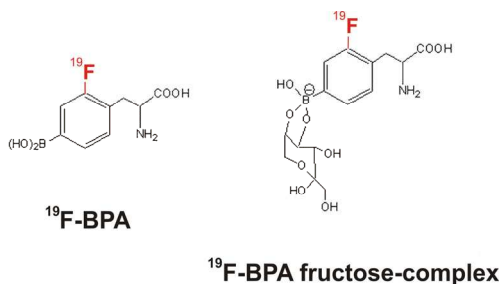


Fig. 4. Chemical structures of ¹⁹F-BPA and ¹⁹F-BPA-fr complex.

Specifically, selective bio-distribution (Fig. 5.) (Porcari et al., 2008; 2009) of ¹⁹F-BPA-fr complex in C6 tumour-bearing rats as compared with normal brain has been demonstrated using ¹⁹F MRI. In addition, a better understanding of ¹⁹F-BPA pharmacokinetic was achieved because of the correlation between the results obtained by using both ¹⁹F MRI and ¹⁹F MRS methodologies. Indeed the correlation between ¹⁹F MR monitoring on rat brain over 4h after ¹⁹F-BPA-fr complex infusion and the quantification of ¹⁹F spectra collected from blood samples showed a maximum uptake of ¹⁹F-BPA in C6 glioma at 2.5h after infusion. Thus, 2.5h after infusion is the optimal time of neutron irradiation according to previous results (Hsieh et al., 2005) obtained by using PET measurements of ¹⁹F - BPA.

These findings suggest the potential future application of ¹⁹F MRI and ¹⁹F MRS using ¹⁹F-BPA in clinical trials. Indeed, the correlation of both techniques allows the mapping with the high spatial resolution characteristics of MRI of the distribution of ¹⁰B compounds and at the same time to follow the pharmacokinetic of ¹⁰B agents. Moreover, since ¹⁹F NMR can be performed using an ¹H MR scanner by suitably tuning RF coils, only minor improvements in the MRI clinical scanner are required for future clinical applications.

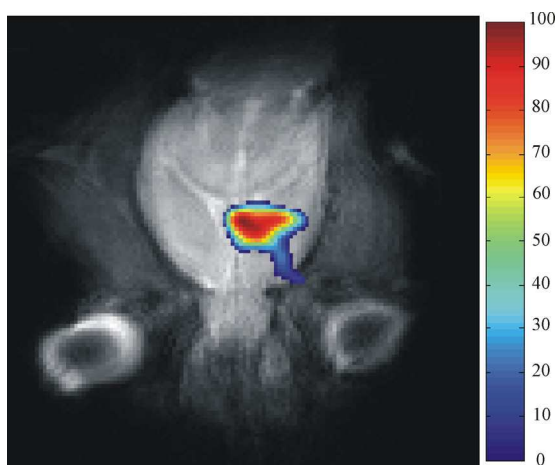


Fig. 5. ¹⁹F-BPA-fr complex bio-distribution map in C6 glioma model at 2.5h after infusion (Porcari et al., 2008)

5. Conclusion

It is apparent from previous sections that BNCT is one of the most complex therapeutic modalities for brain tumour treatment. Due to the lack of progress in developing more effective treatments for high grade gliomas, the main challenge for BNCT in the near future, is to become a clinically useful treatment modality. Our work in optimizing the therapy has just this aim. Our research has been focused in overcoming some of the major limitations of BNCT effectiveness.

Firstly, in order to improve ^{10}B accumulation within the tumour, we demonstrated, both *in vitro* and *in vivo*, the potential of L-DOPA to enhance tumour uptake of BPA (Capuani et al., 2008, 2009). The most interesting findings of this work were the increased BPA tumour uptake *in vitro*, with C6 glioma cells, as well as *in vivo*, with C6 glioma model. Indeed, the L-DOPA preloading increased the BPA intracellular accumulation in C6 glioma cells 5 times with 4-hours of L-DOPA incubation (Capuani et al., 2008). The BPA tumour uptake in C6 glioma model (Capuani et al., 2008) increased 2.7 times. Interestingly, there was no increasing of BPA uptake in a normal brain. These stimulating results encourage the potential use of L-DOPA in BNCT of brain tumours because of L-DOPA ability to induce a significant enhancement of BNCT effectiveness without remarkable associated side effects. Moreover, the use of L-DOPA in BNCT clinical trials could be also facilitated because of its long-standing clinical use as a treatment for Parkinson's disease.

In order to determine the optimal irradiation time improving the BNCT efficiency, ^{19}F MR imaging and spectroscopy methodologies were proposed for investigating the pharmacokinetics and bio-distribution of BPA (Porcari et al., 2008; 2009). The correlation between both imaging and spectroscopic results obtained on glioma model highlights a better understanding of ^{19}F -BPA uptake either in the tumour or in systemic circulation confirming evidence of maximum BPA uptake within the tumour at 2.5 hours after infusion (Porcari et al., 2008). These results demonstrate that both ^{19}F MRI and ^{19}F MRS are feasible and practical methodologies with potential future clinical application. Indeed, ^{19}F NMR can be performed with an ^1H MR clinical scanner with only minor hardware and software improvements. Both of the solutions proposed to improve BNCT effectiveness will help the therapy to overcome its main hindrances to become a clinically useful modality in the near future.

6. Some standard abbreviations and symbols

^{10}B	Boron-10 isotope
BBB	Blood Brain Barrier
BNCT	Boron Neutron Capture Therapy
BPA	<i>p</i> -boronophenylalanine
BPA-fr complex	<i>p</i> -boronophenylalanine-fructose complex
Br:Bl	brain-to-blood
BSH	sodium borocaptate
^{14}C	Carbon-14 isotope
γ rays	gamma rays
ICP-AES	Inductively Coupled Plasma-Atomic

^{19}F -BPA	Emission Spectrometry
^{19}F -BPA-fr complex	fluorinated analogue of BPA
^{19}F -MRI	^{19}F -BPA-fructose complex
^{19}F -MRS	Fluorine Magnetic Resonance Imaging
^{19}F -NMR	Fluorine Magnetic Resonance Spectroscopy
GBM	Fluorine Nuclear Magnetic Resonance
^1H , ^2H	Glioblastomas Multiforme
^4H	Hydrogen isotopes
2	Alpha particle
HPCL	High Performance Liquid Chromatography
^7Li	Lithium-7 isotope
L-DOPA	L-3,4-dihydroxyphenylalanine
LET	Linear Energy Transfer
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MRSI	Magnetic Resonance Spectroscopy Imaging
n^{th}	thermal neutron
^{14}N , ^{15}N	Nitrogen isotopes
NMR	Nuclear Magnetic Resonance
p	proton
PET	Positron Emission Tomography
σ	cross-sections
RBE	Relative Biological Effectiveness
T:BI	tumour-to-blood
T:Br	tumour-to-brain
WHO	World Health Organization

7. Acknowledgment

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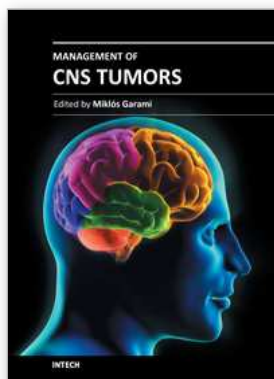
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