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Can Lithium Salts Herald a New Era for Neutron Capture Therapy?

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Glioblastoma multiforme (GBM[a]) is the most common primary malignant tumor of the central nervous system.[1] GBM not only is an aggressive disease but also has proven resistant to all forms of conventional treatment. The median survival time for patients is approximately 14 months even after radical surgical resection followed by concurrent radiotherapy and chemotherapy,[2] and the 5-year survival rate for patients with the disease is approximately 3%.[1] Boron neutron capture therapy (BNCT) was first proposed by Locher[3] in the 1930s, and it has been investigated in several countries as an experimental treatment for the treatment of GBM for over 5 decades and, more recently, other tumors such as malignant melanoma.[4] BNCT is normally referred to as a "binary therapy" as it makes use of two key components that can be manipulated independently. One of the components is the nonradioactive ^{10}B isotope which possesses a large, effective neutron capture cross-section (3838 barns). ^{10}B has the unusual capacity to capture low-energy thermal neutrons (the second component) and undergo a fission process that results in the formation of high linear energy transfer (LET) particles ($^4He^{2+}$ and $^7Li^{3+}$) and approximately 2.4 MeV of energy. Because of the short path lengths of $^4He^{2+}$ and $^7Li^{3+}$ ions (9 and 5 μm, respectively), these nuclei are confined only to the tumor cell in which they originated. Numerous clinical studies have clearly demonstrated the safety of BNCT in the treatment of GBM, and its efficacy is at least comparable to the best of conventional radiotherapy.[4] However, several clinical trials around the world, other than those in Japan, Argentina, and Italy, have now been discontinued for a variety of reasons and the therapy is considered by some observers to lie at the crossroads.[4−6] It appears that a significant paradigm shift is required in order to realize the full potential of BNCT as a frontline treatment for GBM and other tumors.

One major issue associated with BNCT is the limited efficacy of the two boronated agents that are used clinically, namely, 4-L-boronophenylalanine (BPA) and the ionic B_{12} cluster compound commonly known as borocaptate (BSH) (Figure 1). More recently, combination therapy using both agents has proved to be much more effective, as each can target a different subpopulation of tumor cells leading to differential uptake and accumulation mechanisms.[7] Despite this quite significant advance during the past few years, it is clear that BNCT requires a significant change in direction if it is to be ever considered as a standard treatment for GBM. Indeed, there is some skepticism in the medical fraternity regarding the ultimate therapeutic potential of BNCT, and its future as a viable therapy for high-grade gliomas has been questioned.[8]

The development of new agents for BNCT is, like traditional pharmaceutical agents, a time-consuming and challenging process requiring great research effort and expense. The development of agents that can deliver significant quantities of ^{10}B ($\sim 10^9$ B atoms) to each tumor cell and at the same time remain relatively low in toxicity, i.e., by preferentially targeting tumor rather than healthy cells, is a Herculean task, as every clonogenic cell needs to incorporate sufficiently high concentrations of ^{10}B. Indeed, despite the fact that several different classes of boron agents have been discovered and evaluated over the past 2 decades, none has yet to enter clinical trials; BPA was the last agent to be successfully introduced into the clinic over 20 years ago when it was originally used for the BNCT of malignant melanoma.[9] More recently, gadolinium neutron capture therapy (GdNCT) has been proposed as a possible alternative to BNCT. It makes use of the nonradioactive ^{157}Gd isotope with its immense effective neutron capture cross-section (255 000 barns),[10−12] the largest of all the naturally occurring isotopes and 66 times greater than ^{10}B. Although Gd(III) complexes are widely used in the clinic as MRI contrast agents, no clinical trials in GdNCT have ever been conducted. Despite some promising leads,[11,13−16] much basic research remains to be completed particularly in relation to tumor targeting, as the key products of the GdNC reaction are Auger and Coster−Kronig electrons which have a very limited range (about several nanometers), and thus, the Gd must be delivered in proximity to important biomolecules such as chromosomal DNA.[11,15,17]

^6Li (942 barns, natural abundance of 7.4%) is another nonradioactive isotope that, like ^{10}B, can undergo neutron capture resulting in an effective fission reaction which leads to the formation of high LET particles ($^4He^{2+}$ and $^3H^+$) and a tremendous amount of energy (~4.78 MeV). The generation of radioactive $^3H^+$, a β-emitter, may lead to safety concerns in a human patient, but the amount produced during the neutron capture reaction has been estimated to equate to approximately 1% of the maximum permissible body burden and is not thought to be a major issue if a typical NCT treatment protocol is followed.[12]

Li^+ is a small, chemically unreactive alkali metal ion that cannot be incorporated readily into tumor-selective agents.

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[a] Abbreviations: BNCT, boron neutron capture therapy; BPA, 4-L-boronophenylalanine; BSH, sodium borocaptate; GBM, glioblastoma multiforme; GdNCT, gadolinium neutron capture therapy; GSK-3, glycogen synthase kinase-3; LET, linear energy transfer; NCT, neutron capture therapy.

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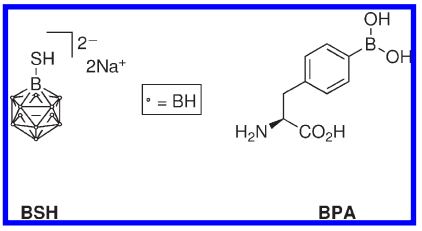

Figure 1. Structures of sodium borocaptate (BSH) and 4-L-boronophenylalanine (BPA).

The use of Li^+ in medicine (in the form of simple salts such as Li_2CO_3) for the treatment of bipolar disorder has been well-established over the past 60 years, but its mechanism of action is still unclear.[18,19] A likely mode of action involves a competition between Li^+ and Mg^{2+} ions for binding sites in several Mg^{2+}-dependent enzymes and proteins owing to the similar physicochemical properties shared by the two cations, e.g., ionic radii.[18] It is clear that an understanding of the underlying biomolecular mechanism(s) for Li^+, e.g., its diffusibility and cell membrane permeability, is also of great relevance to LiNCT. The safety of Li salts in human cancer patients for potential application in NCT has only been investigated in one seminal study conducted back in 1956,[20] the details of which are provided below. Indeed, only three other publications detail the potential use of Li in NCT and all were published prior to 1956 when only rudimentary experiments involving crude neutron sources and tumor-bearing mice were possible.[21−23] It is clear that with access to many diverse types of boron compounds, optimized neutron beams, and the greater effective neutron capture cross-section of ^{10}B over ^6Li, all efforts over the past 5 decades have focused on BNCT which has now become almost synonymous with NCT. But with all the focus to date directed toward BNCT, can LiNCT ever be considered as a viable option in the treatment of high-grade gliomas? For this question to be answered, a few key points need to be addressed.

One important question is whether there exists any evidence of Li^+ being taken up by glioma cells at all. Although no mention was made of its potential relevance to NCT, in a landmark paper published over 35 years ago by Gorkin and Richelson,[24] Li^+ uptake in glioma cells was clearly demonstrated and, importantly, a significant level of intracellular Li^+ was found in C6 rat glioma cells in vitro. Li has also been shown to affect the growth and division of C6 glioma cells by diminishing their clonogenic potential and also inhibiting the G2-M phase of the cell cycle.[25] Another more recent study has even demonstrated that when compared to a human neuroblastoma (SH-SY5Y) cell line (a good model for adrenergic neurons because it can be differentiated into a neuronal phenotype), human glioma cells were found to accumulate significantly greater quantities of Li^+ at an apparently faster rate over the same time period.[26]

Perhaps a more important question is whether high Li^+ levels can ever be achieved in vivo in order to pass a therapeutically useful threshold for NCT and whether such levels can be tolerated by patients. Typically, Li salts are administered to bipolar patients in a safe manner at doses where plasma concentrations usually lie in the range 0.5−1.2 mmol L^{-1}.[18] The half-life of Li^+ in the brain is significantly longer than that found in the serum,[27,28] and importantly for LiNCT, a substantial fraction of the Li^+ is located intracellularly.[29] Moderate toxic effects including apathy, tremors, and restlessness are observed at higher Li levels approaching those of ^{10}B (e.g., the typical plasma level of BPA in BNCT patients is approximately 2.5 mmol L^{-1})[30,31] with serious side effects observed in minor cases (e.g., ataxia, renal dysfunction, seizures, and coma).[32] Whereas these toxicities cannot and should not be underestimated, such side effects could be managed adequately in a hospital setting, particularly as the administration of ^6Li salts would only be conducted just prior to neutron irradiation rather than on a long-term basis as is normally required for the management of bipolar disorder. This possibility was clearly demonstrated in Sweet's pioneering paper regarding the dosage and safety thresholds of Li salts,[20] namely, LiCl, in GBM patients. Notably, LiNCT experiments were never conducted in this work, probably because of the unavailability of ^6Li-enriched salts at that time. First, it is clear from the results of Sweet et al.[20] that far greater amounts of LiCl can be administered intravenously to (even critically ill) glioma patients than is normally used to control bipolar disorder, with 180−200 mg kg^{-1} appearing to be feasible when the administration is accompanied by general anesthesia, antiemetic agents, and intravenous saline. No serum analyses were reported in this work, but as a comparison, healthy patients administered only 500 mg (*not* mg kg^{-1}!) of Li_2CO_3 intravenously over 1 h had a peak serum concentration reaching 0.93 mmol L^{-1}.[33] Sweet and co-workers also reported that the average localization factor in GBM when 5000−6000 mg of LiCl was administered to patients over a period of 10−60 min was ~6.2 and it persisted for 3−4 h after administration,[20] a significantly higher differential between tumor and normal tissue than is found for either BPA or BSH.[4]

There are some additional potential benefits that may arise from the use of Li salts in the treatment of high-grade gliomas. A very recent study involving mice has determined the effects of Li in the management of brain metastases from primary cancer outside the brain, but ironically, its role is one of radioprotection of healthy cells from high-energy X-ray photons rather than the destruction of tumor cells by the capture of thermal neutrons.[34] In other words, there exists the intriguing possibility of first treating GBM patients with neutron irradiation to exploit the neutron capture properties of the ^6Li nucleus within tumor cells followed by conventional radiotherapy to exploit the radioprotective effects of Li^+ ions, a fraction of which would also be localized in normal, healthy cells. A related approach involving both conventional radiotherapy and neutron irradiation of patients treated with a combination of BPA and BSH has shown some promise in the BNCT of newly diagnosed GBM.[35] A recent report also shows that Li salts possess potent inhibitory effects toward the invasiveness of glioma cells and may be the direct result of inhibition of glycogen synthase kinase-3 (GSK-3),[36] an enzyme that appears to play a key role in cancer cell migration processes. Interestingly, it has been shown that cancer mortality and incidence are inversely proportional to the Li dose in human patients.[37] All these studies point to possible additive or synergistic effects if ^6Li salts were to be used in NCT.

In conclusion, it is clear that Li salts may play several important roles in the future treatment of cancers such as GBM, but much further research is still required. With the many successes of Li agents in the clinic for the treatment of bipolar disorder over the past 60 years and, furthermore, the safety of these salts now clearly established, a well-planned clinical trial for LiNCT or, alternatively, a combination (ternary) therapy involving BSH and/or BPA with ^6Li-enriched salts is certainly worthy of further investigation.

Indeed, the safety and efficacy of a ^{6}Li or combined ^{6}Li−^{10}B strategy could be determined with minimal effort and expense based on the clinical protocols already used for the BNCT of high-grade gliomas. In the latter case, there exists the exciting possibility that Li may finally unshackle BNCT from the chains of limited efficacy and transform it into a viable treatment for intractable tumors such as GBM. It would certainly be remarkable if, after numerous clinical studies in several countries spanning 5 decades, BNCT was always meant to be a ternary rather than binary therapy or indeed if ^{6}Li salts themselves were found to be superior NCT agents to BPA and BSH, the only clinical ^{10}B agents assessed to date.

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Biography

Louis M. Rendina received his B.Sc.(Hons I) and Ph.D. degrees from the Australian National University. His current research interests lie in the area of bioinorganic medicinal chemistry, in particular the development of new B and Gd agents for neutron capture therapy (NCT) and the use of boron clusters as pharmacophores in medicinal chemistry. He is the recipient of two prestigious national awards from the Royal Australian Chemical Institute (RACI) for his seminal contributions to the areas of medicinal chemistry (RACI Biota Medal for Medicinal Chemistry) and organometallic chemistry (RACI Organometallic Chemistry Award), the only individual to have ever received both awards. He has been elected as a Fellow of the RACI (FRACI, C. Chem.) and a Fellow of the Royal Society of Chemistry, U.K. (FRSC).

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