GLOBAL CLINICAL EXPERIENCE WITH BORON NEUTRON CAPTURE THERAPY (BNCT)

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Abstract. Boron neutron capture therapy (BNCT) represents a top therapeutic method that relies on knowledge in the area of nuclear technology as well as on medicine experience in treating malignant tumour. Various pre-clinical experiments have been initially applied in order to demonstrate the effectiveness of BNCT concept. Once they demonstrated the concept, pre-clinical experiments continued by focusing on a better establishment of the irradiation parameters in each facility, in view of acquiring dosimetry systems, a treatment plan and, most importantly, the development of boron compounds that fit, as best as possible, the ideal BNCT requirements. The first clinical trials focusing on Boron neutron capture therapy were initiated by Dr. Sweet şi Brownell (Massachusetts Institute of Technology - MIT Boston) and Farr (Brookhaven National Laboratory – BNL) in 1951. Between 1951 and 1961, patients with glioblastoma from USA were irradiated, both at BNL as well as MIT. Based on the support provided by EORTC the first BNCT clinical studies were also initiated in Europe. Consequently, EORTC formed a study group for BNCT. A first phase I trial included 25 patients with optimally operated glioblastomas in 5 neurosurgery centres. Another EORTC protocol studied BSH and BPA administration in patients with different types of solid tumours in order to identify new targets for BNCT. Simultaneously, another study following BNCT and BPA in cutaneous metastases of malignant melanoma was implemented. A fourth protocol was initiated for BNCT with BSH in glioblastoma multiforme. A third tumour type approach was based through BNCT therapy and neck cancer. The first studies were established by Kato in Japan. In September 2003, Hiratsuka treated a recurrent papillary thyroid cancer with BNCT, in Japan. Yanagie and collaborators also used BNCT in Japan in recurrent rectal cancers. Other BNCT experiments evaluated treatment methods for locally recurrent breast cancers. Multiple liver metastases of the colorectal adenocarcinoma were among the first liver tumours that raised researchers' interest, from the area of BNCT. In February 2005, in Kyoto, Japan, at KUR the first patient with hepatocarcinoma was treated with BNC. The project “Study, research and application in the oncological clinical practice of treatment with neutron capture by B-10” participated in 2005 at the CEEX governmental competition- “Research Excellency Programmes”. The project was selected for financing and benefitted from a grant offered by the Romanian Government, PC-D01-PT11-94 - 2005. Although there are still considerable inconveniences, BNCT may be regarded as a promising method for cancer treatment.

Keywords: radiotherapy, BNCT, clinical applications

Introduction

BNCT represents a top therapeutic method that relies on nuclear technology knowledge, chemistry, biology as well as on medicine experience in treating malignant tumours.

In 1936, GL Locher (Pennsylvania SUA) suggested, for the first time, that neutron capture reactions could have applicability in cancer therapy. [1,2]

Various pre-clinical experiments were initially applied in order to demonstrate the effectiveness of BNCT concept. Once they demonstrated the concept, pre-clinical experiments continued by focusing on a better establishment of the irradiation parameters in each facility, in order to develop dosimetry systems, a treatment plan and, most importantly, the development of boron compounds that fit, as best as possible, the ideal BNCT requirements. Furthermore, pre-clinical experiments were carried out for different tumours than head tumours, some of them already being continued in the area of clinical research.

Experimental BNCT irradiation on pre-clinical models:

BNCT irradiation on murine subjects for head and neck tumours formed the subject of several researches.
in Osaka, Japan and Bariloche, Argentina,[3,4] that obtained an important rate of complete remission. In Argentina, studies were carried out with the purpose to evaluate feasibility of BNCT sequential irradiation (two successive applications), thus constituting the first researches of this kind.

Other animal subjects were used for BNCT irradiation of pancreatic tumours,[5] thyroid tumours [6], mesothelioma intrathoracic tumours[7], or multiple lung metastases (Taormina Project in Pavia, Bariloche in Argentina), prostate tumours [8], ocular melanoma [9], osteosarcoma (TAORMINA), etc.

For primitive tumours of the liver or metastatic ones o series of pre-clinical trials was applied in order to identify the optimal dosimetry and treatment plan [10,11,12] as well as an experimental irradiation of laboratory animals (Pavia, Bariloche). [13, 14]

BNCT based clinical trials

The first clinical trials on neutron Boron capture therapy were initiated by Sweet and Brownell (Massachusetts Institute of Technology - MIT Boston) [15, 16, 17] and Farr (Brookhaven National Laboratory – BNL) [15, 18] in 1951. Between 1951 and 1961, patients with glioblastoma from USA were irradiated, both at BNL as well as MIT however without conclusive results which rendered, at the time, the trials a failure. In 1967-1985 Prof. Hatanaka from Japan obtained impressive outcomes, which triggered more research in the field. [19] Studies were resumed both in USA (in 1994 at Brookhave and Massachusetts Institute of Technology for glioblastomas and malignant melanoma, by using BPA) [20,21] as well as in Europe (in 1997 la Petten – glioblastoma- BPA and BSH).[22] Subsequently, similar studies began in Finland (1999- glioblastoma, ENT and malignant melanoma- BPA)[23], Czech Republic (2000-glioblastoma- BPA and BSH)[24], Sweden (glioblastoma-BPA and BSH) [25] and Italy (2001- liver metastases-BPA), Argentina (2003- malignant melanoma_ BPA) [26] and Taiwan (2010- ENT- BPA).[27] In Japan since 1968 until now patients with glioblastoma, malignant melanoma, head and neck cancer, pulmonary cancer, thyroid and liver cancer patients have been irradiated with therapies based on both BPA and BSH.

Hatanaka and later on, his collaborator, Nakagawa [28] irradiated over 200 patients suffering from glioblastoma, predominantly using BSH. They reported promising results on a long term due to the extended survival period achieved by certain of their patients. Thus, survival rates were: at 2 years- 11.4%, at 5 years- 10.4% and at 10 years- 5.7%.[19, 28] Results were not confirmed by sub-group tests performed by Laramore on American patients treated by Hatanaka.[29] Despite this, the Japanese experience with BNCT therapy in glioblastomas was positive, enabling further development of this treatment technique. The difference between the first American and Japanese studies lied in the Japanese practice, namely an initial debulking surgery and subsequent irradiation with thermal neutrons following craniotomy (direct brain irradiation) considering the low penetrability of thermal neutrons. [30, 31]

Once studies were resumed in the United States, approximately 53 patients were irradiated at BNL and 20 at MIT, by using BPA and epithelial neutrons, with higher tissue penetrability. [32, 33] The results were comparable to those from the conventional irradiation. [30, 34, 35]

More recent protocols are currently trying to improve BNCT technique by prolonged BPA infusion for better tumour penetrability (Sweden) [36, 37], by mixing BPA with BSH (Japan)[38, 39, 40, 41, 42], mixing thermal and epithelial neutrons [43] or combining with X-ray irradiation boost. [38] So far the outcomes seem superior to the classical BNCT irradiation.

Based on the support provided by EORTC, the first BNCT clinical studies were also initiated in Europe. Consequently, EORTC formed a study group for BNCT. A first phase I trial included 25 patients with optimally operated glioblastomas in 5 neurosurgery centres. They received 4 daily consecutive BNCT fractions at European High Flux Reactor in Petten. These studies aimed at determining immediate and late toxicities and to compare them with toxicities occurring to conventional radiotherapy of 60 Gy in six weeks. Another EORTC protocol focused on BSH and BPA administration in patients with different types of solid tumours in order to identify new targets for BNCT. Hence, another study on the administration of BNCT combined with BPA was in cutaneous metastases of malignant melanoma. A fourth protocol was initiated for BNCT with BSH in glioblastoma multiforme. [44]

In Europe, a smaller number of patients with glioblastoma was treated: in Petten, Holland (27 patients), [22, 24], Essen Germany (24 patients) [45], Helsinki Finland (20 patients) [23], Studsvik Sweden (52 patients) and Rez Czech Republic (5 patients). [22]

After brain tumours, the most predominant in terms of number of irradiated patients was malignant melanoma, the experiments having begun back in the 1980s. The first patients were irradiated by Mishima in 1985 and the outcomes turned even better than those in brain tumours, as complete remissions were registered and some of the patients having no sign of illness four years after the irradiation. [46, 47, 27, 48, 49] Busse et All also treated patients with brain metastases occurring to malignant melanoma or cutaneous melanoma.[20, 30, 50]. Patients with malignant melanoma were also irradiated in settings in Argentina.[51] The overall conclusion was that BNCT in irradiation of malignant melanomas obtained better outcomes compared to glioblastomas, BNCT constituting an experimental treatment method recommended in inoperable tumours that cannot benefit from stereotactic radiosurgery.[52]

A third tumour approached through BNCT was recurrent mouth and throat cancer. The first studies were carried out by Kato in Japan [53-55], followed by other Japanese researchers including Kankaanranta in Finland.[56] Kato irradiated 26 patients with recurrent head and neck tumours that had received both radiotherapy and chemotherapy. Histological patterns were heterogeneous, this including even salivary gland sarcoma or adenocarcinoma. The mean period of survival was 13.6 months but with a survival rate of 24% at six years. Significant adverse events occurred, such as cerebral necrosis, osteomyelitis, mucositis.[53]
Kankaanranta and collaborators deployed a clinical study that included 30 patients with recurrent head and neck cancers that received BNCT with BPA therapy in Helsinki.[56] 29 of patients were evaluable for the rate of response, which led to 13 complete remissions and 9 partial remissions, a 76% rate of response with 20% rate of survival, with no progression at 2 years and 30% global survival at 2 years.[35, 56, 57] The most frequent adverse events were oral mucositis, pain and fatigue. Three patients presented osteoradionecrosis and 1 patient showed soft tissue necrosis.[56]

In Japan, Fuwa N. et All tried to improve results from BPA administration both intravenously as well as though the arteries in the case of ENT cancers. They irradiated 5 patients that had no other therapeutic option. For two of the BNCT irradiation had to be applied two times. The medical team obtained one complete remission and 4 partial remissions, but except for one patient the rest died to a recurrent illness. For such cases the authors suggest conventional irradiation mixed with a BNCT boost.[58] In August 2010, the first patient with recurrent ENT cancer was irradiated in Taiwan.[27]

The role of BNCT in ENT cancers continues to be relatively inconclusive considering the low number of patients treated so far.[59]

In September 2003 Hiratsuka treated with BNCT therapy the first recurrent papillary thyroid carcinoma, in Japan. In 2009 the patient was alive with no signs of recurrence and with well tolerated treatment.[60, 61]

In Japan, Yanagie and collaborators used BNCT for recurrent rectal cancers but with no reports on long term results.[62]

Other BNCT experiments assessed treatment methods for locally recurrent breast cancer.[63]

**BNCT experience in liver tumours**

Primitive liver tumours are one of the most frequent tumours in the world. Of these, 25-30% are hepatocarcinomas and the rest come from intrahepatic bile ducts. The mortality rate to this cancer type is very high, but varies, at global levels. The incidence of these tumours is increasing worldwide, along with the increase of viral hepatitis B and C. The liver represents is the most common metastatic site in malignant tumours (colorectal, breast cancers, pulmonary, etc). For example, 10-25% of colorectal patients have liver metastases at the time of diagnosis and of them only 25% can be resected with curative intent. For most patients, therapeutic options are limited, with little satisfactory results.

Multiple liver metastases of colorectal adenocarcinoma were the first to raise interest of researchers in the area of BNCT. [22, 24] Thus, through the TAORMINA project, two patients underwent irradiation at the Pavia University reactor.[64] They received BPA- fructose 300 mg/kg i.v. for two hours through the colic vein, after which hepatectomy was performed. The liver was irradiated with BNCT, outside the body, with thermal neutrons of 4 x 1012 cm-2 fluency, for 10 minutes. Consequently, during the second surgical phase, the liver was transplanted back to the patient. [65] The first patient, aged 48 was treated in 2001. He presented 14 bilobal metastases and 63% residual liver function, with no vascular abnormalities. The procedure spanned on 21 hours, of which, 5 hours and a half anhepatic. 7 days after the procedure the patient went through another surgery, this time for blood collection in the peritoneal cavity. The first three weeks succeeding BNCT the patients presented liver and kidney failure and rhabdomyolysis, with accentuated asthenia and brain dysfunction, probably through cell lysis. Kidney dialysis was necessary for two weeks. After the first month the patient reached full recovery, with an increase in the liver residual function of 73%. [64] 20 month after BNCT the first local recurrence resurfaced, the patient undergoing surgery and adjuvant chemotherapy that he previously had refused. 33 month after BNCT the patient presented a new hepatic and extrahepatic relapse that was non-responsive to chemotherapy. 40 month post BNCT a new immunochemotherapy protocol is initiated but with no response which led to the patient’s death in August 2005. In 2003 the procedure was applied to a second 39 year old patient. He presented 11 liver metastases, 58% residual liver function, dilated cardiomyopathy and a hepatic artery vascular abnormality. The procedure lasted 18 hours and 40 minutes, of which 6 hours and 10 minutes anhepatic. The first post BNCT month went similarly as with the previous case, this meaning the same evolution in the liver, kidney, brain functions. 30 days postoperatively, surgery was needed in order to correct a hepatic artery thrombosis but it failed. The patient died 33 days after BNCT to cardiac failure and pulmonary oedema caused by the hepatic artery thrombosis.

In February 2005, the first patient with hepatocarcinoma was treated in Kyoto, Japan, at KUR. The patient was diagnosed in June 2004 when resection was performed. In November 2004 he presented multiple bilobar recurrence which led to a transarterial chemoembolization. In December 2004 another relapse was identified. A combination of 250 mg/kg BPA was administered in 60 minutes as well as BSH 1g/kg, a share of it associated with lipiodol. After six hours the patient was irradiated for 62 minutes with a lateral right beam and for 21 minutes with a posterior beam. In terms of adverse events, fever and cytolysis occurred but disappeared after one week. Sadly, one month after BNCT administration, progressive disease was identified having the patient die 10 month post BNCT.

BNCT experience in primitive or secondary liver tumours is, for the time being, limited requiring a complicated methodology that impedes its administration on a large scale, hence the formulation and release of clear conclusions. [67]

**Conclusions**

Although BNCT is an innovative and promising treatment method, still several aspects continue to be critical which prevent it from being applied on a larger scale. The first problematic aspect regards the boron delivery compound. The second aspect has to do with the neutron flux. The third concerns dosimetry and last but not least, clinical experience is essential. In what concerns the latter aspect, a multidisciplinary team can be difficult to form. Furthermore, researchers have to deploy numerous and complex clinical trials that include
a larger number of patients before ranking BNCT therapy in cancer treatments.

Thanks to the support provided by EORTC the first clinical studies on BNCT in Europe were deployed.

The project “Study, research and application in the oncological clinical practice of treatment with neutron capture by B-10” participated in 2005 at the CEEX governmental competition- “Research Excellency Programmes”. The project was selected for financing and benefited from a grant offered by the Romanian Government, PC-D01-PT11-94 - 2005. Research was carried out by a 5 partners’ consortium: "Prof Dr. Al. Trestioreanu” Oncology Institute, Bucharest (IOB), "Fondeni” Clinical Hospital (ICF), “Pitesti” Nuclear Research Department (SCN), “Horia Hulubei” National Institute for R&D in Physics and Nuclear Engineering (IFN-HH) and “Victor Babes” Institute's Foundation.

The project was conducted over four years in 6 stages. Despite the mentioned inconveniences one can conclude that BNCT is a promising treatment method for cancer and research in this domain represents the first stage in the implementing process of an effective oncology therapy in Romania. One of the physical accomplishments of BNCT could be the application of Cyclotron/Laser from the Magurele platform as long as a neutron flux is obtained as well as an irradiation medical site.

References


2. Locher G.L., Biological effects and therapeutic possibilities of neutrons – Am J Roentgenol 1956; 36 (1); 1-13.


42. Miyatake S, Kajimoto Y, Kawabata S et al, Modified boron neutron capture therapy for malignant gliomas performed using epithermal neutron and two boron compounds with different accumulation mechanisms: an efficacy study based on findings on neuroimages – J Neurosurg. 2005, 103: 1000.


