Start-Up of the First In-Hospital Neutron Irradiator (IHNI-1) & Presentation of the BNCT Development Status in China

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Abstract

The paper presents the BNCT basic development and status in China in the past four decades achieved by nuclear research organizations, hospitals and enterprises. The development process includes tests and verifications to the NCT fundamental rationality, researches to stem cells of brain glioma, the BNCT effect research to brain glioma, establishment and start-up of the first In-Hospital Neutron Irradiator (IHNI-1) and arrangement of clinical supporting system to the IHNI-1. The BNCT pre-clinical irradiation and research will be executed when the beams parameters measurement and beams performance with phantoms are obtained.

Keywords: Brain Glioma, BNCT, In-Hospital Neutron Irradiator (IHNI-1), Thermal Neutron Beam, Epithermal Neutron Beam, Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES), Prompt Gamma Ray Neutron Activation Analysis (PGRNAA), Clinical Trial

1. Introduction

The BNCT development in China started from the 70s of the last century when the annual incidence of brain glioma exceeded 50,000 cases. At that time, there were many difficulties in treatment of brain glioma as technology of CT and MRI offered little help to accurate diagnosis of the nature of brain glioma and non-tumor discrimination. The disease induced great concerns of our nuclear science researchers and neurosurgeons. In China, SU started first research work to the growth and differentiation of brain glioma cells on medical basis, sorted out reasons for resistance of brain glioma cells to radiotherapy and chemotherapy, and inferred applicability of the BNCT in brain glioma treatment. FMMU carried out researches to the BNCT effect using models of the Chinese brain glioma cell series. All these studies and researches have shown BNCT's positive effect, however, the further clinical experiment could not be followed due to unavailability of suitable neutron source. Among many research reactors of various types in China, none of them is able to provide a specified neutron beam exclusively designed for BNCT's clinical researches and trials with little investment and in short time.

Thanks to its years of efforts, CZEC has finally worked out the overall framework design of the IHNI-1, which is specially done for BNCT purpose. With the support and guidance of CNNC plus the active and devoted involvement of CZEC, CIAE, NINT, BAPCMI and, BCTC, etc. the construction of the IHNI-1 financed by GCG was completed and realized its criticality by the end of 2009 in the courtyard of the CIAE. The IHNI-1 is designed on the basis of China Miniature Neutron Source Reactor, which can be seated in the hospital, the 30kW facility is able to set up two neutron beams of different energy fields for irradiation, and enjoys features of inherent safety, easy operation and low construction cost. The IHNI-1 creates an effective platform, which escalates China BNCT development from fundamental researches to the step of clinical researches and trials. The site of the IHNI-1 is 2km away from the supporting hospital, (Hospital affiliated to CIAE), where hospital supporting systems matching for the BNCT clinical researches and trials are in installation progress.

2. The Experimental Verification on NCT Rationality

The CIAE has carried out the following research works for simulating productions of BNCT by using α particles and ^{7}Li ions produced by radioactive source ^{241}Am and the HI-13 tandem accelerator respectively:

2.1 The plasmid DNA solution is irradiated by α and ^{7}Li, and then the DNA fragments are analyzed by Atomic Force Microscopy (AFM). The results show that the mean length of DNA fragments decrease as the dose increases. The fractions of linear and open

circle DNA molecules increment goes in line with the dose rise. Compared with α particles, ^{7}Li ions demonstrate a stronger relative biological effect.

2.2 The plasmid DNA in the presence or absence of Mannitol (scavenger of free radical $OH^{\cdot}$) is irradiated by ^{7}Li ions or γ rays. The result verified that, the DNA strand breaks induced by ^{7}Li ions is the common contribution of direct effect and indirect effect of free radical and quite a fraction of DSB induced by direct ionizing energy deposition of heavy ions, which cannot be eliminated by Mannitol.

2.3 The SH-SY5Y cells (human neuroblastoma cell lines) are irradiated also by ^{7}Li ions. By means of the clone-forming method and flow cytometry, the damage effects of neurocytes are analyzed. The cells survival fraction in the consequence of ^{7}Li irradiation reduces obviously when compared with γ rays irradiation, and distribution of cell cycle shows that the cell arrest take place in G2/M cell cycle irradiated by ^{7}Li.

2.4 Recently the investigation to biological effect on boron-loaded human brain glioma U251 cells, rat glioma C6 cells and primarily cultured rat atrocities, in which boron has been loaded, irradiated by thermal and epithermal neutrons at IHNI-1 is in progress.

3. Series Studies on Human Gliomas

Suzhou University initiated studies on human glioma in the following three stages:

3.1 The First Stage (1975-1990)

The first human glioma cell line and its transplantation mouse model NHG1 were established. Then the hybridoma monoclonal antibody SZ39 was produced along with the cell line establishment, which was used in the research on biological target therapy against glioma after labeled with ^{131}I, ^{35}S and immunoconjugated with adriamycin.

3.2 The Second Stage (1991-2004)

Researches were focused on the cell differentiation and differentiation induction of glioma cells. Gene expression profile associated with tumor cell differentiation was established and CDC2 was proved to have closed relationship with initiation and progression of glioma.

3.3 The Third Stage (2005-)

Serial researches on human brain glioma stem cells (hBGSCs) have been performed since 2005. First, hBGSCs were isolated from SHG44 cell line and clinical specimens of primary and recurrent gliomas. Four cell lines were established named SU1, SU2, SU3 and SU4, respectively[-]. SU3 was transfected with RFP and transplanted into RFP nude mice. The results showed: (1) hBGSCs had the potential of transdifferentiation into vascular endothelial cells and played important roles in tumor neovascularization. (2) hBGSCs could fuse with host cells and participate in the tumor tissue remodeling. (3) hBGSCs indicated strong resistance potentiality to radiotherapy and chemotherapy due to the expressing DNA repairing gene ATM and ABCG2 respectively.

4. BNCT Effective Study on Human Glioma Cells

The FMMU and NINT treated U87, U251 and SHG44 glioma cells *in vitro* by BNCT with L-BPA as the boron carrier and the neutron source at Xi'an Pulsed Reactor (XAPR) as the irradiation rays. The relative biological effect of BNCT on cells, especially apoptosis induction, was assessed and the possible mechanism was discussed.

4.1 Boron Uptake

^{10}B were uptake as expected into SHG44, U87 and U251 cells after incubation of 24 hours in the medium with 50 μg/ml ^{10}B. Then, the boron concentration in cells were gradually raised up to 2.72±0.25 μg/10^{7}cell, 9.78±0.49 μg/10^{7}cell, 2.48±0.34 μg/10^{7}cell, for SHG44, U87 and U251 cell, respectively.

4.2 *In Vitro* Irradiation

In vitro irradiations of three cell lines were carried out by using the neutron source at XAPR reactor. *In vitro* γ ray irradiations were carried out by a ^{60}Co γ source in the FMMU. Cells were divided into nine groups. At the beginning of the experiment, all the cells were in exponential phase of growth and with a density of 3×10^{5}/ml. The components of the reactor neutron source and ^{60}Co γ source are shown in Table 1.

Components		Dose Rate (Gy/min)
Dose Rates for the Reactor Neutron Source	Thermal Neutron	1.04×10^{-3}
	Epithermal Neutron	2.48×10^{-4}
	Fast Neutron	1.07×10^{-1}
	γ-ray Photon	1.57×10^{-2}
	$^{10}B(n,\alpha)^{7}Li$	5.09×10^{-4}/ ppm^{10}B
Dose Rates for the ^{60}Co γ-ray Source		1.40×10^{1}

Table 1: Dose Rates for Reactor Neutron Source and 60Co γ Source

4.3 Proliferation Assays

Cell survival was determined using the 3-(4,5-dimethylthiazol-2yl-2,5-diphenyltetrazolium (MTT) assay. Inhibitory effect of BNCT on proliferation of U87 cells were much more significant

than that of γ ray ($p<0.05$). The inhibitory effect was marginal in 4 Gy and 8 Gy γ ray groups, while significant inhibition was observed in BNCT 4 Gy and BNCT 8 Gy group. The number of U87 cells slid after treatment of 48h in the 6 groups mentioned above in which most potent inhibition was determined in group of BNCT 8 Gy. Similar effects were observed in SHG44 and U251 cells.

4.4 AnnexinV/PI Method

The apoptotic rate of U87 cells in BNCT 8 Gy and BNCT 4 Gy group was significantly higher than that in their counterpart group of γ ray ($P<0.05$). Moreover, the apoptotic rate in BNCT 8 Gy was even higher than that in BNCT 4 Gy group ($P<0.05$). Similar effects were observed in SHG44 and U251 cells.

4.5 Western Blot Analysis

Bcl-2 regulated mitochondrial pathway, which is mediated by noxious stimuli that ultimately lead to mitochondrial injury and apoptosis, is a major pathway of apoptosis cell signaling. Bcl-2 and Bax, as two main member of Bcl-2 protein family, function as anti-apoptotic and pro-apoptotic factor in tumors respectively. After BNCT, Bcl-2 expression was decreased while the Bax level was raised. The down-regulation of Bcl-2 protein and up-regulation of Bax after BNCT treatment demonstrated that the function of BNCT may be mediated by damage of mitochondrial membrane integrity.

5. Startup of the IHNI-1

IHNI-1 is low power research reactor designed and manufactured by BCTC and CIAE for BNCT on basis of Miniature Neutron Source Reactor (MNSR) developed by CIAE.

Thermal neutron beam and epithermal neutron beam are designed on both sides of the reactor core, opposing each other. , A small thermal neutron beam is specially designed for the measurement of blood boron concentration by the prompt gamma neutron activation analysis (PGNAA).

5.1 Description of Facilities

The reactor thermal power of undermoderated core and pool-tank type is 30 kW, with 12.5% ^{235}U of UO_2 as fuel, light water as coolant and moderator, and metallic beryllium as reflector. The fission heat produced in the reactor is removed by the natural convection. The final loading is 302 fuel rods. Fig. 1 shows the structure of INHI-1, more details can be found in Reference [1].

5.2 Experimental Results

After erection of all the IHNI-1 components including fuel, Be reflector, detectors, two neutron beams facilities, etc., startup of IHNI-1 can be realized. The following experimental results were obtained during the startup of IHNI.

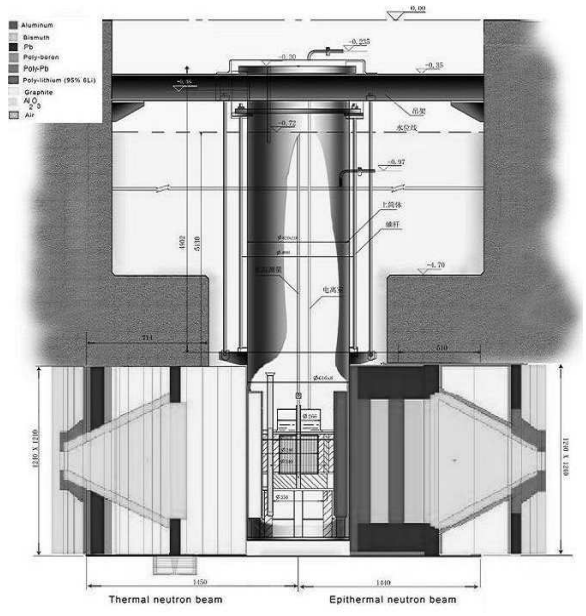

Fig. 1 The Structure of the IHNI-1

✧ Critical Experiment

Two ways of extrapolation and insertion were used for the measurement of critical water level. The results are 25.4 liter with the water temperature of 17º, and without water in the pool and external neutron source. Adding water to the designed water level of vessel and pool, the reactivity was measured on periodic basis, the total reactivity is 4.85 mk. The reactivity regulator is inserted into beryllium annulus at the depth of 20 mm from the surface of beryllium bottom disc, the reactivity was measured again, the verified value is 4.2 mk, which was in compliance with the definition given in design.

✧ Power Excursion Experiment

Safety of the IHNI-1 relies on a limited maximum excess reactivity control in all the normal and abnormal conditions. When a certain amount of positive reactivity is inserted into the reactor promptly, the power will be increased rapidly, however, it will turn to the normal value due to the negative temperature effect.

Fig. 2 shows the curve of power transient, the maximum peak power value for 4.2 mk reactivity release is 85 kW, the corresponding time is 229 s.

✧ Maximum Operation Time at Full Power

At the full power of 30 kW, the IHNI-1 can be operated for 12 hours continuously, and the perturbation of the power level is about 3‰.

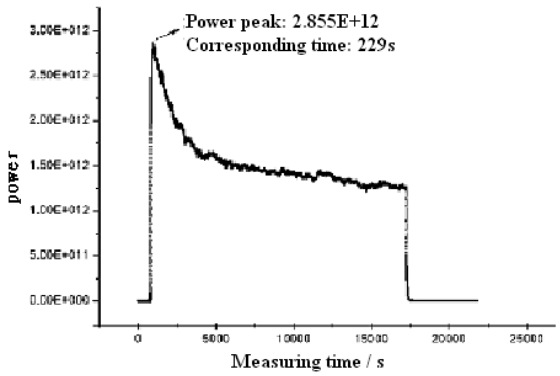

Fig.2 Power Transient Following 4.2 mk Step Increase in Reactivity

The IHNI-1 operation time can meet the BNCT clinical request, the reactivity release shows that the IHNI-1 has inherent safety. The parameters for neutron beam port will be measured in the next step of work.

6. Medical Support System (MSS)

MSS for the IHNI-1 clinical application is mainly prepared by Hospital No. 401 affiliated to CIEA. In addition to the clinical facilities necessary for the BNCT application, the MSS setup is specially designed for convenience of Boron Concentration measurement and utilization of Treatment Plan Software. A special measurement beam and Analysis Room of the IHNI-1 are designed for the purpose of Blood Boron Concentration real-time PGRNAA measurement. The available ICE-AES Analysis System in Chemical Analysis And Experiment Center in the CIAE in the vicinity of the hospital can be used for pre-clinical studies. Moreover, BIAPCM's Monte Carlo Dose Calculation software (MCDB) [2] for preparation of Treatment Plan shall be used in the MSS for clinical radiation dosimetry evaluation. The MCBD is able to automatically work out 3-D reconfiguration of the patient with a calculation speed 3.4 times faster than that of the MCNP. The MCBD can meet clinical requirement for the NCT calculation time (<2CPU hours and the error <4%).

7. Conclusion

According to the IHNI-1 project schedule, measurement of neutron fluence rate and gamma dose rate distribution in the air at two neutron beam ports will be conducted in 2010, then the radiation dosimetry evaluation to beam performance by means of using the simplified rectangular plexiglass phantom and ellipsoidal sphere brain phantom will be performed. The optimized values of AD, ADDR and AR will be used as the fundamental basis for the future BNCT clinical application.

References

Zhou Yongmao, Li Yiguo, et al. 2006, Design and construction of the In-Hospital Neutron Irradiator-I, Proceedings of ICNCT, 557-560.

Deng L. Li G. Chen C.B., 2007. MCDB Monte Carlo Code with Fast Track Technique and Matrix Mesh Tally for BNCT. J Nucl. Sci. Tech. 44(12), 1518-152