Fast reactor neutrons in the treatment of malignancies and perspectives of NCT and NCT enhanced fast neutron therapy in Obninsk, Russia

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Medical Radiological Research Center RAMS during long time collaborate with other Institutions at Obninsk, Russia, in development of different neutron techniques. Main collaborator is Institute for Physics and Power Engineering. Reactor BR-10 was used for fast neutron therapy of patients with different malignancies during long time. Obtained clinical experience gives possibility to propose new approach to neutron-capture therapy: combination of neutron-capture therapy with photon therapy. Now IPPE in collaboration with other centers modernize KG-2.5 accelerator for neutron capture therapy and fast neutron therapy. Project of medical block construction at reactor WWRc (Institute of Chemical Physics, Obninsk) are developed. Beginning of experimental investigations at these facilities is planned to the end of 2004.

Introduction

Obninsk is the first "city of science" in Russia. Many Obninsk Institutions deal with different aspects of neutron technologies. During long time Medical Radiological Research Center RAMS (MRRC RAMS) and Institute for Physics and Power Engineering (IPPE) collaborate in the creation of new techniques of neutron therapy. Big experience in using fast reactor neutrons for the treatment of patients with different malignancies has obtained. The creation of new medical complex for neutron capture therapy (NCT), fast neutron therapy (FNT) and in NCT enhanced FNT is planned. Previous experience gives possibility to propose new approach for these techniques.

Materials and Methods

From 1985 up to 2002 more than 450 patients with different malignancies have treated in MRRC RAMS with fast reactor neutrons [1]. Most of them had locally advanced or recurrent tumors. The source of fast neutrons is reactor BR-10 (IPPE) with mean energy of neutron beam after special filter from 1 cm of boronated polyethylene about 1 MeV. The distance from active zone of reactor to patient is about 10 m. The field size can be changed from 4 by 4 to 10 by 10 cm with help of special medical collimator. Laser and field light are used for patient positioning.

Mixed photon-neutron techniques with contribution of fast reactor neutrons in total dose 20-40 % are developed and are evaluated. Unfortunately, reactor BR-10 was closed for dismantling in 2002. It stopped investigations in FNT and in NCT enhanced FNT [2]. The beam with characteristics close to BR-10 neutron beam can be obtained at reactor WWRc (Institute of Chemical Physics (ICP), Obninsk). Project of medical block construction at reactor WWRc are developed. The modernization of KG-2.5 accelerator (IPPE) allows to receive beam for NCT and, in perspective, for FNT. The creation of medical facility for NCT and FNT on the basis of accelerator KG-2.5 (IPPE) is planned [3]. Beginning of experimental investigations at these facilities is planned to the end of 2004.

Results obtained in patients with head and neck tumors are most important from point of view of future NCT investigations in patients with brain tumors. Long time results are analyzed in 133 patients with squamous cell carcinoma of head and neck up to now. More than 90 % of them have locally advanced or recurrent tumors.

Split-course of radiation therapy was used in patients with laryngeal carcinoma. Neutron therapy in daily dose 0.2-1.4 Gy was provided to total neutron dose 2,0-5.6 Gy at first stage of treatment. Relative biological effectiveness (RBE) of neutrons was 3.5-5.0 depending from fraction size. Then conventional photon therapy to equivalent dose 32-40 Gy was provided. Evaluation of local reactions and tumor regression at this dose was done. Complete and partial tumor response were basis for continuation of conventional photon therapy to equivalent dose 52-60 Gy. Radical surgery was provided in case of no tumor response after first stage of treatment.

In patients with primary and recurrent tumors of oral cavity and oropharynx other radiation therapy technique was used. Neutron therapy in dose 1Gy was provided three times per week to total dose 3-4Gy (RBE=4). Then conventional photon therapy to equivalent dose 56-60 Gy was done. Tumor response was evaluated one month after finishing of radiation therapy.

Results and Discussion

Serious late local radiation complications (Grade III) rate is only 7 % in patients with primary laryngeal carcinoma, 6 % in patients with primary carcinoma of oral cavity and oropharynx and 11 % in patients with recurrences of carcinoma of oral cavity and oropharynx. It was perichondritis in patients with laryngeal carcinoma, osteoradionecrosis and ulcer of mucosa in patients with tumors of oral cavity and oropharynx.

It is well known that one of the major problems of neutron therapy is the development of severe late local radiation complications. Developed techniques of mixed photon-neutron therapy are well tolerated by surrounding tumor normal tissues. In the same time these techniques are effective. Only in 27 % of patients with laryngeal carcinoma no tumor response was registered after first stage of radiation therapy. Five-year actuarial local control rate in patients with primary laryngeal carcinoma after radical course of mixed photon-neutron therapy is 63 % and 73 % after combined therapy (mixed photon-neutron therapy at first stage and, then, radical surgery). Five-year actuarial local control rate in patients with primary carcinoma of oral cavity and oropharynx is 51 %. Complete response rate after mixed photon-neutron therapy is 57 % in patients with recurrences of carcinoma of oral cavity and oropharynx. One-year actuarial overall disease-specific survival rate in patients with recurrent tumors of oral cavity and oropharynx is 82 %.

The evaluation of all clinical experience and radiobiology studies allows to do some conclusions about further development of NCT:

1. Combination of BNCT with photons and in perspective with other kinds of irradiation (for example, protons) is promising and must be thoroughly investigated. Such combination improves conditions of treatment. Conformal photon therapy allows to minimize radiation dose to surrounding tumor normal tissues, to improve dose distribution and to decrease the risk of radiation complications. Optimal combination of BNCT and photons is BNCT at first stage of treatment and afterwards photon therapy. Especially important it is in situations when impossible to control concentration of ^{10}B in tumor and surrounding tissues exactly and at Phase I investigations when the risk of radiation complications is high.

2. Clinical targets for BNCT at the first stage of clinical investigations are tumors with bad results after conventional radiation therapy. First of all they are brain tumors (glioblastoma multiforme and anaplastic astrocitoma) and melanoma. Other candidates for BNCT are adenocarcinomas of different localizations. Generally speaking, these are tumors with big doubling time. In future, other opportunities of BNCT must be investigated. For example, very perspective can be BNCT in patients with different metastases (sarcoma of bone, soft tissue e t.c.) due to big difference in characteristics of metastases and surrounding metastases normal tissues from point of view biochemistry and, as a result, in ^{10}B concentration ratio.

3. Due to absence of long time and big clinical experience in BNCT (one exclusion is Hatanaka data), drugs for BNCT with optimal clinical characteristics (big ^{10}B concentration ratio between tumor/normal tissues, stable and high concentration in tumor, minimal toxicity, easy monitiring of ^{10}B concentration in tissues) best location of tumor for Phase I investigations is superficial.

4. Despite all criticizm of some modern investigators concerning Hatanaka data, retrospective analysis of them gives possibility to conclude that BNCT can improve clinical results at least in selected group of patients with brain tumors. Hatanaka developed original technique of intraoperative BNCT. It has many clinical limitations which are connected with necessity to secure optimal conditions for operation and BNCT in reactor area. In modern situation epithermal neutron beams allow to provide BNCT after surgery in postoperative period without removing part of skull. In perspective, in situation with location of medical accelerator for BNCT at medical hospital the idea of intraoperative BNCT can receive new impulse for further development.

5. The problem of low BNCT efficacy can be connected with bad vascularazation of some parts of tumor. This problem can be solved by BNCT fractionation, using combination of BNCT with conformal photon or proton therapy, using other elements (for example, Gd) for neutron-capture therapy (NCT). The uncertainty of ^{10}B concentration in tumor and brain tissues is the reason of radiation complications development risk. Combination of NCT with conventional photon therapy gives possibility to optimize total dose and to decrease risk of complications.

Obninsk has good perspectives for creation of medical facilities for NCT and FNT. Project of medical block at reactor WWRc (ICP) was finished last year. We hope that obtained in cooperation with IPPE scientists experience gives us the possibility to create specialized medical facility for NCT and FNT on the basis of accelerator KG-2,.5 this year. It allows to provide dosimetric and preclinical studies. The accelerator as the source of neutrons for fast neutron therapy and BNCT in perspective can be installed directly in medical center. It gives the possibility to accelerate clinical investigations in BNCT, to decrease limitations for general status of patients, to improve possibilities for combined and complex treatment. The reactor has much more strong limitations for his installation in city from point of view of environmental safety. That is why accelerators have better clinical perspectives in this area of radiation therapy.

Taking in consideration the experience of MRRC and IPPE in boost BNCT of recurrences and metastases of melanoma, best way for beginning of clinical approbation of KG-2.5 after modernization is the treatment of such group of patients with developed earlier at reactor BR-10 technique. Of course, clinical approbation of KG-2.5 will be done only after thorough dosimetric study and radiobiology investigations on cells and animals.

After finish of this stage of work we plan to begin Phase I-II investigations at BNCT in patients with brain tumors and melanomas.

References

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