Therapy at HIMAC

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1. INTRODUCTION

The HIMAC (Heavy Ion Medical Accelerator in Chiba) facility is the first heavy-ion synchrotron complex dedicated to medical use in a hospital environment. As a part of 'the Comprehensive 10-year Strategy for Cancer Control' begun by the Japanese Government in 1984, the project for construction of the HIMAC was carried out at National Institute of Radiological sciences (NIRS), Science and Technology Agency. In November of 1993, the construction of the entire facility was completed and in June 1994 the first patient was treated with 290 MeV/u carbon-ions. The aim of our heavy-ion clinical trials on various type of malignancies is to establish clinical advantages of heavy-ion in cancer treatment.

2. RATIONALE OF HEAVY-IONS IN RADIOTHERAPY

Heavy-ions have a benefit of superior depth-dose localization allowing selective irradiation to the tumor while minimizing irradiation to the surrounding normal tissues. In addition, the peak-region of heavy-ions have several biological advantages for tumor control:

a) A reduced oxygen enhancement ratio (OER). The radioresistance of the tumors could be due to the presence of hypoxic tumor cells. Normal tissues are usually considered to be well-oxygenated. Differential effects are expected that favor the tumor tissues.

b) An increased radiobiological effectiveness (RBE). The clinical effect of heavy-ions is more advantageous in fractionated scheme than in single treatment, because the sublethal and potential lethal damage caused by high-LET radiation is less able to be repaired.

c) A reduced susceptibility to variations in radio-sensitivity in the cell cycle. The part of the tumor radioresistance could be due to the presence of the tumor cells in radioresistant phases of the cell cycle, especially in slow growing tumors.

3. HISTORY OF HIGH ENERGY HEAVY ION BEAMS

At the beginning of 1940's, Dr. C.Tobias was already tried to accelerate carbon nuclei using the 60-inch cyclotron at Berkeley/California. This was the origin of the heavy ion therapy. In 1950 he proposed the idea of using a linear accelerator as an injector to a cyclotron for producing high-energy heavy ions. In 1974 the heavy ion linear accelerator (HILAC) and the Bevatron were connected together (BEVALAC) to accelerate heavy ions to energies suitable for heavy ion radiotherapy at LBL. Between 1979 through 1993 nearly 300 patients were treated with chiefly neon-ions. The patients were selected for treatment when their tumors were not expected to respond favorably to conventional irradiation. Castro et al. reported that, compared with historical data, improved results were observed in selective tumor types including salivary gland tumors, paranasal sinus tumors, advanced bone and soft tissue sarcomas, locally advanced prostate carcinoma and biliary tract carcinoma. Unfortunately, the clinical trials at LBL were discontinued due mostly to financial difficulties. Thus more study is expected in the HIMAC trial, especially for the tumor which exhibited favorable results at LBL.

4. SELECTION OF HEAVY ION BEAMS FOR CLINICAL APPLICATION

The carbon ion beams were selected in the initial clinical studies for the deep-seated tumors, because the carbon ion beams appeared to have the most optimal characteristics in physical and biological efficiencies compared with other heavy ions, and the RBE value of carbon-ion-peak was similar to the fast neutron therapy which has also been used at NIRS. In carbon ions, the effects of an elevated RBE are produced only in the SOBP-region. Therefore, the ratio of dose in the peak region relative to plateau region will be maximized and more effective biological dose localization will be expected. This phenomenon enhances with the use of fractionation schedule.

5. PRECLINICAL STUDIES

Preparatory to starting radiotherapy on human cancers, variety of preclinical studies have been carried out to confirm the quality of carbon-ion beams for clinical application.

a) In order to verify the precision of the treatment planning system for calculation of depth dose distri-butions, dosimetries were performed in monkeys and phantom materials.

b) Using 290 MeV/u carbon-ions, we have performed preclinical studies on five human cell lines cultured in vitro and mouse skins to estimate RBE values relative to photons and fast neutrons. The RBE values relative to

Co-60 at the 6cm SOBP have been in the range of 1.5-3.5 depending upon location of the peak, fraction size and number of fractions. In single dose irradiation on cultured cells, the RBE values at 10% survival ranged 1.2-2.3 at the proximal (40KeV/μ) and 2.0-2.7 at the distal part (82KeV/μ) of the SOBP. In the treatment regimen of 4 fractions in 4 days, the RBE values along the 6cm SOBP for mouse skin dry desquamation were 2.3 at the proximal and 3.2 at the distal part of the SOBP.

6. CLINICAL TRIAL ORGANIZATION

In order to perform clinical trials most effectively, phase I/II clinical protocols have been designed for each tumor site. We have organized an advisory committee, ethical committee and each protocol working group, which consists of interdisciplinary group of scientists invited from other cancer centers and university-hospitals as well as those of NIRS. We have also an ethical subcommittee consists of NIRS staffs to evaluate the eligibility of each patient referred to us as a possible candidate for heavy ion treatment.

7. DESIGN OF CLINICAL TRIALS

Since our initial trials are directed to the toxicity of heavy ions on normal tissues together with initial estimate of tumor response, locally advanced and/or medically inoperable localized carcinomas have been chosen.

a) In head and neck tumors the locally advanced and/or recurrent tumors being treated unsuccessfully with other treatment modalities are chosen. Histologically, the radioresistant tumors such as adenoid cystic carcinoma or melanoma are accepted. The patient who merely refuses surgical treatment would not be acceptable for this study.

b) For brain tumors, malignant glioma including glioblastoma multiforme, anaplastic astrocytoma, and lesser grade astrocytoma are treated. Malignant gliomas are initially irradiated by 50Gy/5 weeks. of x-ray with concomitant use of chemotherapy (ACNU), which is followed by carbon ion irradiation to the gross tumor volume. Lesser grade astrocytomas are irradiated with carbon ion alone to a T2 high signal area in MR-images.

c) For lung tumors, carbon ion therapy are applied to stage I tumors (T1-2N0M0) which are inoperable due to medical reasons. In medically inoperable non-small cell lung cancer (NSCLC) with stage I, the 5-year survival rate after radiotherapy using photon is only 25-30%. The marked increase of treatment results can be expected with the application of heavy ion-therapy.

d) Primary hepatocellular cancer (HCC) is selected for T2-4N0M0 tumors. The criteria for patient selection are similar to those for head and neck cancers, in that the patients selected for carbon ion therapy would have to be difficult with other available modalities.

e) In cervical cancer intracavitary irradiation combined with external treatment is very effective. Therefore, stage IIIB and IVA with large tumors more than 4cm in diameter are chosen for this trial, because the most of them are usually hard to cure with conventional modalities.

f) Prostate cancer has been chosen as one of the most suitable subjects for carbon-ion therapy, and the patients with stage B2 or C and pN0-2 are chosen. The existence of pelvic lymph nodes metastasis is surgically resected and confirmed, and then hormone therapy is given for 2-3 months before heavy-ion therapy.

g) In esophageal cancer, locally advanced T3-4 cases are selected radically or preoperatively. In preoperatively irradiated cases, the histological effects of carbon-ion therapy can be obtained.

h) The medically inoperable and/or recurrent sarcomas of the bone and the soft tissue are chosen. These tumors are usually so-called radioresistant and the promising treatment results were obtained in fast-neutron therapy.

We have also a phase I/II protocol to search for an optimal dose-fractionation schedule and a suitable site for carbon-ion therapy.

As the patients should ethically be treated first with conservative doses, the initial doses employed are determined to be 10-20% lower than those possibly tolerable for skin and musculo-connective tissues. In this phase I/II study, the doses will be escalated by 10% increments for every 3-5 patients based on careful attention to skin, mucosal, and neurological reactions as well as observation of tumor response.

8. PRELIMINARY RESULTS OF TREATMENT

Between June 1994 through May 1996, a total of 124 patients were treated with carbon ions. Of then, 55 patients were entered in analysis who had a minimum follow-up of 6 months.

The dose levels which were given to 55 patients analyzed in this study are summarized in Table 1. The doses were escalated by 10% only when any type of major complications was not encountered. For brain tumors, it was recommended to treat larger number of patients with the initial conservative dose level because the CNS may have substantially higher RBE values to high-LET radiations than for other tumor sites. The RBE values for late CNS effects is estimated to be 4.5-5.0 from several fast neutron studies.

Table 1. Tumor Response in Patients Treated with Carbon-ions from June 1994 through August 1995

Site	Dose (GyE)	No.of cases	Primary response CR	PR	NC	PD
Head & neck	48.6	3	0	3	0	0
	54.0	3	0	1	1	1
	59.4	4	3	0	1	0
Tongue	55.8	2	0	1	0	1
Brain: Astrocyt.	50.4	3	0	0	3	0
Malig.gl.	66.8*	7	0	0	5	2
(*photon 50Gy)						
Lung: stage I	59.4	4	0	3	1	0
	64.8	4	0	1	3	0
	72.0	3	0	1	2	0
stage IIIA	59.4	2	0	2	0	0
Liver	49.5	2	1	0	1	0
	54.0	3	0	2	0	1
Prostate	54.0	2	0	2	0	0
Uterine cervix	52.8	3	3	0	0	0
Miscellaneous	48.0					
	-52.8	8	0	2	4	2
Total		53	7	18	21	7

(response rate=47%)

Table 2 shows the early and late radiation-related morbidities after carbon-on therapy. All but two patients were able to complete the planned treatment, and no patient developed major radiation-related morbidities. The treatment of two patients with head and neck cancer was incomplete because of progressing disease in an unirradiated region (one case) and intolerable fungus infection of the oral cavity (one case). Anterior died of distant metastasis 2 months after treatment and posterior died of gross bleeding of the primary tumor 10 months after treatment. At each dose level and tumor site, the skin reactions ranged from light to moderate erythema at the acute phase (within 3 months after the beginning of treatment) and none to slight pigmentation at 6-18 months after treatment. It is interesting to note that compared to skin reactions the mucosal reactions appeared to be smaller.

The primary responses of 55 patients were demonstrated in Table 1. In 12 cases with locally advanced cancer of the head and neck region, a complete response (CR) was obtained in 3 patients, and a partial response (PR) in 5 patients. Then the response rate was 67% (8/12). At present, 9 patients are alive and well with no evidence of tumor regrowth or radiation-related complications. In the brain tumors, no patients had any evidence of radiation necrosis on CT or MRI at the time of this analysis. In every patient, the shrinkage of the tumor shadow was small to none.

In malignant gliomas 3 patients died of uncontrolled tumor. In all, the primary response of the brain was unsatisfactory probably due to the inadequate given dose. 11 patients with non-small cell lung cancer in stage I were treated. 10 were adenocarcinomas and one had squamous cell carcinoma. Irradiation was given to the primary lesion only but not to the regional lymphatic area. At 6-18 months after treatment, radiographic findings demonstrated patchy to dense fibrosis in almost every patient on CT images or chest x-rays. However, no patients developed any subjective symptoms from radiation-related pneumonitis or fibrosis. Among 11 patients the response rate of the tumor (CR+PR) was observed in 5 patients and slight reduction (NC) in 6 patients. At the time of this analysis, the regrowth of primary tumor after carbon ion therapy was observed in 3 patients, probably due to insufficient total dose. In 10 cases with the hepatoma, prostate cancer, and the locally advanced cervical cancer, a complete response (CR) was obtained in 4 patients, and a partial response (PR) in 4 patients. The response rate was impressive, particularly in locally advanced cervical cancer.

Table 2. Normal Tissue Morbidity in Carbon-ions Treated between June 1994 through August 1995

Site		Grade *									
		Early (<3 months)					Late (>6 months)				
		No.	0	1	2	3	No.	0	1	2	3
Skin											
Total		55	4	30	21	0	47	13	33	1	0
				(grade 3=0)						(grade3=0)	
H & N		26	3	8	15	0	19	11	7	1	0
Chest	14	0	8	6	0		14	0	14	0	0
Abd.	15	1	14	0	0		14	2	12	0	0
Mucosa	11	7	2	2	0	9	7	2	0	0	
Lung		14	10	2	0	2	13	11	1	1	0
G.I. tr.		7	6	1	0	0	7	7	0	0	0
Bladder	7	6	1	0	0	7	7	0	0	0	

*=according to RTOG(<3mo.) and RTOG /EORTC (>6mo.)

Although the number of patients analyzed and the follow-up period are both too small, and although the radiation doses employed may be too conservative, the preliminary results do appear to demonstrate promising effects of carbon-ion radiotherapy for various kinds of malignant tumors, except the malignant gliomas. Even though we gave the lowest possible dose for cancer control, the local control for them was satisfactory with no evidence of radiation-related complications. The tumor response of malignant gliomas, however, was not satisfactory, possibly because of inadequate total dose

9. FUTURE DIRECTIONS OF HEAVY ION THERAPY:

At present, the HIMAC-projects are being carried out to demonstrate that in what type of tumors the heavy-ion therapy is more effective than the usual photon therapy and proton therapy. One of the key factors in radiotherapy for achieving cancer cure is dose localization, which has been proven effective with improved local control obtained by such modalities as brachytherapy, intraoperative radio-therapy, 3D-conformal radiotherapy etc. In this regard, heavy-ions could deliver biologically more effective dose to tumors. Therefore, it is strongly expected that the heavy-ion therapy offer increased cure rates in cancer therapy, because it possesses a combination of radiobiological and dose localization advantages. In principle, for the tumors that are found to be treated better with fast neutrons than with conventional radiations, heavy-ions should be superior to fast neutrons because of their good localization capabilities, similar to the proton beams.

There are numerous tasks that should be done for successful performance of heavy-ion therapy. For example, we decided to use carbon-ions first, but in the next stage silicon or argon-ions will be selected for relatively superficially located tumors.

The most important mission of HIMAC project is to find out the appropriate role for heavy ions in radiotherapy. An international collaboration should be extensively established for conducting our HIMAC-study.

10. SUMMARY:

The phase I/II study of HIMAC heavy-ion therapy was started at NIRS in June 1994. For this study, treatment protocols for various tumor sites were designed to assess the toxicities as well as the tumor responses of carbon-ion therapy by escalating doses for each tumor site. In this report 55 patients with a minimum follow-up of 6 months were analyzed. None of the patients experienced any type of major radiation-related morbidities. Although the number of patients analyzed and follow-up periods are too small, and the radiation doses employed may be too conservative, the preliminary results appear to demonstrate promising effects from carbon-ion therapy.