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Introduction

The potential of heavy ion therapy for clinical use in cancer therapy stems from the biological parameters of heavy charged particles, and their precise dose localization. Biologically, carbon, neon and other heavy ion beams (up to about silicon) are clinically useful in overcoming the radioresistance of hypoxic tumors, thus increasing biological effectiveness relative to low-LET xray or electron beams. Cells irradiated by heavy ions show less variation in cell-cycle related radiosensitivity and decreased repair of radiation injury. The physical parameters of these heavy charged particles allow precise delivery of high radiation doses to tumors while minimizing irradiation of normal tissues. Clinical use requires close interaction between radiation oncologists, medical physicists, accelerator physicists, engineers, computer scientists and radiation biologists. (9,13,22,23)

In 1975, a collaborative clinical study was begun between University of California San Francisco Medical Center (UCSF) and UCLBL to determine the efficacy of heavy charged particles in the treatment of human cancers. Helium and neon ions were selected to be clinically tested, representing relatively low-LET ions (helium) for their dose-distribution advantages and high-LET (neon) for both its biological and physical advantages. The preliminary experience at LBL (1,2,3,4,5,6,7,8,26) has confirmed the usefulness of heavy charged particles in increasing tumor dose relative to normal tissues. Effective doses 10-35% higher than possible with standard techniques have been achieved with helium and neon ions and significant improvement in local control and survival rates have been demonstrated compared to historical results.

Treatment Planning and Delivery

3-D treatment planning is required for accurate charged particle therapy, using CT and MRI scanning as the prime methods of tumor localization and target volume delineation (12). After initial evaluation which includes a careful history and physical examination, an individually constructed immobilization device to hold the patient in the desired treatment position was made, generally from perspex or thermoplastic splinting material (polyform). A planning CT scan and/or MRI was performed with patient in the immobilization device and in treatment position whenever possible. At LBL, a CT scanner was installed to scan the patient in either prone, supine or upright position. For MRI scans, a supine scanning position had to be used. To accommodate the different position, techniques for image correlation and data transfer techniques were developed at LBL to assist in treatment planning (12,13,20).

The final charged particle treatment planning was based on the CT scan, using the computerized treatment planning system developed at LBL (12). Custom made beam shaping devices and tissue compensators were designed and fabricated for each individual portal. Alignment aids such as digitally reconstructed beam portal radiographs and templates were created using the treatment planning system. Treatment planning for heavier ions such as carbon or neon must also take into account the fragmentation tail. LET and RBE values are different in each portion of the beam profile and must be assessed in some meaningful way to plan for normal tissue late effects. Some specialized tissues have higher RBE values than skin and other tissues. The central nervous system tissue has an RBE value for neon ions of 4.5 compared to megavoltage irradiation and for the gastrointestinal tract, the RBE may also be elevated at about 3.5 .

At LBL, the 184" synchrocyclotron and Bevatron were utilized in treating with charged particles. The energies used were 215/232 MeV/u for helium ions and 585/670 MeV/u for neon ions. Tumor doses were expressed in physical Gray (Gy) and in Gray equivalent (GyE) by multiplying the charged particle beam physical dose by a factor called the Relative Biological Effect (RBE) which represents the ratio of the photon beam dose to the charged particle beam dose required for the same effect (skin and mucosal reactions). A smaller physical dose of helium or neon ions is needed for a similar effect than megavoltage photons. The use of Gray-equivalent model was an attempt to intercompare units with low-LET irradiation; it was of some value for protons or helium ions but was not as valid or useful for heavier ions such as neon.

The neon ion daily dose was initially about 1.0 Gy per fraction but this was raised to ~3.0 Gy per fraction as experience was gained, and since fractionation does not protect against late effects as is the case for low-LET radiations. The total dose of neon ranged from 20-25 Gy in 4-5 weeks, given 4 days per week.

For neon ions, the RBE utilized ranged from about 2.0 to 3.0 for skin and other tissues, depending on LET in that portion of the beam, and dose fraction size. For the central nervous system, the neon RBE used was 4.5. The RBE of neon for gastrointestinal tissues may also be elevated over skin and other tissue, in the range of 3.0-3.5.

Clinical Results With Heavy Charged Particles

The Phase I-II clinical trial at LBL using neon ions was initially reviewed in 1991 by Linstadt et al.(17). A total of 239 patients who had received a minimum neon physical dose of 10 Gy (median followup for survivors 32 months) were evaluable.

Compared with historical results, the 5- year actuarial disease specific survival (DSS) and local control (LC) rates suggested that neon ion treatment improved outcome for several types of tumors:

Advanced salivary gland carcinoma	DSS 59%	LC 61%
Paranasal sinus tumors	DSS 69%	LC 69%
Advanced soft tissue sarcoma	DSS 56%	LC 56%
Macroscopic sarcoma of bone	DSS 45%	LC 59%
Locally advanced prostate carcinoma	DSS 90%	LC 75%
Biliary tract carcinoma	DSS 28%	LC 44%

The treatment of malignant gliomas, pancreatic, gastric, esophageal, lung, and advanced or recurrent head and neck cancer was not significantly better than low-LET therapy although the numbers of patients treated were small, and there were anecdotal instances of tumor control in all categories.

By May of 1992, a total of 299 patients had completed therapy with at least 10 Gy of neon ions. These patients are still being followed and the results from the previous survey continue essentially as noted above. Some of the highlights are covered below:

Heavy Ion Radiotherapy Of Prostate Cancer

Carbon or neon ion conformal therapy may be beneficial for slowly growing tumors such as locally advanced prostatic carcinoma. Evidence of value in using neutron therapy for prostate cancer has been seen in RTOG trials (24). These high-LET beams offer the possibility of less radiation repair of high-LET injury as well as eliminating some of variations in sensitivity during different phases of the cell cycle. In addition, areas of hypoxia within the tumor which are resistant to low-LET treatment are

less so in the presence of high-LET irradiation. Charged particle conformal therapy has the advantage over neutrons of allowing optimal conformation of the high-dose zone to the target volume, mainly the prostate, seminal vesicles and adjacent lymphatics.

At LBL 23 patients, mostly with Stage C carcinoma of the prostate, have been treated with neon ions. Both local control and survival appear excellent as compared to historical data for this stage of disease. Only 2 patients have died from disease, both from distant metastases. Two patients are scored as having local recurrence, although both are alive. In one patient, a biopsy was obtained three months post completion of radiation treatment, and was followed by orchiectomy and no evidence of subsequent disease. The second patient had a positive biopsy outside of the United States and is apparently free of disease on LH antagonists at 5 years post radiation treatment.

Kaplan-Meier local control and survival are projected at a greater than 90% level at 7 years post treatment in this small group of patients. In this series, high-LET charged particle irradiation appears to show high potential in the treatment of locally advanced prostatic cancer and may diminish the local failure rate from approximately 50% to the level of 10% or less. However care must be taken in delivering this therapy. We have had 3/23 patients with rectal injuries possibly attributable to the neon ion treatment. One patient had a very large tumor and probably too large a volume of anal canal and rectum was treated. Anal sphincter stricture developed leading to colostomy. Another patient developed an anterior rectal wall ulcer leading to a recto-vesical fistula requiring a colostomy and ileal conduit. A third patient had a colostomy following development of a rectal ulcer which appeared inferior to the neon target volume, and may not have been related to the neon ion therapy. These results indicate caution should be used in escalating doses in conformal therapy. A boost of neon ions for locally advanced prostate cancer after pelvic radiation therapy to 45-50 Gy should

probably be in the range of 5-7 Gy or approximately 15-20 GyE, a dose which should offer local control in virtually all patients with a low level of morbidity.

Heavy Charged Particle Irradiation For Unfavorable Soft Tissue Sarcoma

Between 1978 and 1989, 32 patients with unfavorable soft tissue sarcoma underwent light ion (helium, neon) irradiation with curative intent at Lawrence Berkeley Laboratory (17). The tumors were located in the trunk in 22 patients and head and neck in 10. Macroscopic tumor was present in 22 at the time of irradiation. Two patients had tumors apparently induced by previous therapeutic irradiation. The follow up ranged from 4-121 months (median 27 months). The overall 3-year Kaplan-Maier local control rate was 62%; the corresponding survival rate was 50%. The 3-year Kaplan-Maier control rate for patients irradiated with macroscopic tumors was 48%, while none of the patients with microscopic disease developed local recurrence (100%). The corresponding 3-year Kaplan-Maier survival rates were 40% (macroscopic) and 78% (microscopic). Patients with retroperitoneal sarcoma did notably well; the local control rate and survival rate were 64% and 62%, respectively. Complications were acceptable; there were no radiation related deaths , while 2 patients (6%) required operations to correct significant radiation related injuries. These results appear promising compared to those achieved by low-LET irradiation, and suggest that this technique merits further investigation in residual or unresectable sarcoma close to critical structures as in the retroperitoneum, abdomen or pelvis.

Preliminary Results In Heavy Charged Particle Irradiation Of Bone Sarcoma

Between 1979 and 1989, 17 patients with unfavorable bone sarcoma who were treated wholly or in part with heavy charged particle irradiation at LBL were reviewed by

Uhl et al (27). The majority of tumors were located near critical structures such as the spinal cord or brain. Gross tumor was present in all but two patients at the time of irradiation. Six patients were treated for recurrent disease. Histologies included osteosarcoma, Ewing's sarcoma, and recurrent osteoblastoma. The followup ranged from 7 to 118 months (median 40 months). The 5-year Kaplan-Meier local control rate was 48%; the corresponding survival rate was 41%. Over half the patients succumbed to distant metastases despite the majority of patients receiving chemotherapy. From the results of this preliminary study, we believe that heavy charged particle irradiation can be effectively used for control of locally advanced or unresectable bone sarcoma, especially in the skull base, ribs, pelvis or vertebrae.

Irradiation Of Bile Duct Carcinoma With Charged Particles And/Or Photons

A retrospective study by Schoenthaler et al. (25) was performed analyzing all patients with bile duct adenocarcinoma who received radiotherapy at the University of California, San Francisco and at the Lawrence Berkeley Laboratory between 1977 and 1987, a total of 62 patients. UCSF patients received photon therapy (median dose 54 Gy), and LBL patient were treated with helium and/or neon ions (median dose 60 GyE). Forty-eight patients were treated postoperatively with curative intent, 30 with photons and 18 with particles. Thirty-six patients in the study had gross residual disease; none had microscopically negative margins. The overall two year actuarial survival was 28%: 44% for particle treated patients and 18% for patients treated with photons. Median actuarial survival was 23 months in particle patients and 12 months in photon patients. Local control was also improved, though less significantly, in patients treated with particles (median disease free survival 20 mos vs 4.5 mos, $p = .054$). Compared to conventional photon radiotherapy, treatment with postoperative charged

particle irradiation at LBL appeared to offer a survival advantage in this non randomized series.

Charged Particle Treatment of Salivary Gland Tumors

Heavy charged particle radiotherapy is useful for selected head and neck neoplasms, especially glandular tumors such as arising from major or minor salivary glands (10). At LBL, a number of these patients were treated, most with neon ions although helium ions were utilized in some patients because of lack of beam availability. For 21 patients with minor salivary gland tumors invading the skull base, a 5 year Kaplan-Meier local control rate and survival rate of 68% were obtained.

There were 19 patients treated for major salivary gland tumors, many of whom had locally advanced (11 pts) or recurrent (5 pts) tumors, with a 5 year Kaplan-Meier local control rate of 58%, and a 5 year survival rate of 42%. The 2 year local control in the recurrent group was 50% versus 80% in the nonrecurrent patients. Similarly the 5 year survival was 20% in the recurrent patients compared to 50% in the nonrecurrent patients.

Discussion

High-LET charged particles such as carbon, neon or silicon ions have not yet been sufficiently studied to prove or disprove their merits in clinical therapy. Although the majority of patients treated at LBL received neon ions, the carbon ion beam has biological dose localization advantages which are better than protons or neon ions. The ratio of dose in the tumor volume relative to the entrance region is maximized. Quite sharp lateral edges are present and the small fragmentation tail can be dealt within

treatment planning. Enough high-LET is present to provide significant differences in DNA damage, and suppression of radiation repair. These effects are maximized in the tumor by the use of the dose localization secondary to charged particles.

Slowly growing tumors which seem to be effectively treated by high-LET particles include such histologies as salivary gland tumors, prostate gland tumors , biliary tract tumors and some bone and soft tissue sarcoma. Much additional knowledge is needed in understanding the reasons for this and selecting patients likely to benefit from these therapy. For example, adenocarcinoma arising in other sites than head and neck such as lung deserve to be studied. Techniques for predictive assays are continuing to be developed and tested in the clinic. These include tests of tumor growth kinetics, assays for inherent radiosensitivity, assays of tumor hypoxia and assays to evaluate level and site of DNA damage. Combining these approaches may lead to individual patient profiles which will predict who might benefit from high-LET therapy and should receive it. A determined effort should be made to study tumor resistance at the genomic level and search for high-LET mechanisms to over come this resistance.

Another approach of potential merit is the combining of carbon ion therapy with hypoxic cell sensitizers or other radiosensitizing agents; this has been studied preliminarily in pretherapeutic studies and deserves consideration for clinical Phase I trials.

Although no American facility is currently able to produce heavy ions for clinical use, potentially such a medical beam could be produced at the Brookhaven National laboratory. The possibility of heavy ion facilities in France or Italy also exists although remote at the present time. The NIRS HIMAC accelerator in Japan will be ready to begin clinical studies by late 1994. An excellent accelerator at GSI, Darmstadt will also begin clinical trials in 1996 together with the University of Heidelberg Strahlenklinik.

We have not as yet completed enough studies with heavy ions to assess their merits in tumor therapy, and these pretherapeutic and clinical efforts should be continued over the next decade, in order not to miss a possibly highly significant therapy for certain resistant neoplasms.

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