Review Article

Clinical trials for charged particle beam therapy

Fantine N. Giap[1], Huan B. Giap[2], Martin Jermann[3], Bosco Giap[4], Richard P. Levy[2], Erik Blomquist[5]

[1]Southern Methodist University, Dallas, TX, USA; [2]Scripps Proton Therapy Center, San Diego, CA, USA; [3]Paul Scherrer Institute, Villigen, Switzerland; [4]University of California at Los Angeles, CA, USA; [5]Uppsala University, Uppsala, Sweden

Corresponding to: Huan B. Giap, M.D, Ph.D. Scripps Proton Therapy Center, San Diego, CA, USA. Email: hbgiap@gmail.com.

Abstract: Since 1954 when the very first patient was treated at Lawrence Berkeley National Laboratory with heavy-charged particles, more than 100,000 patients in total have now been treated with charged particle beam therapy. During the first several decades of this new modality, charged particle beam therapy was accessible only at a small number of institutions. More recently, however, this therapy has become available at a rapidly increasing number of facilities worldwide. This expansion of the discipline has led to the development of many more clinical trials, designed to optimize particle-beam therapy and to compare the results achieved with those resulting from other treatment methods. Presently, more than 50 clinical protocols worldwide are actively involved in the effort to improve our understanding of these clinical guidelines. The purpose of this brief review is to offer a broad overview of these protocols, highlighting the specific disease categories that are now being studied using proton and/or heavier-ion therapy, and how the parameters of dose-escalation, beam conformity, and RBE modeling are being evaluated for various disease sites and stages.

Key Words: Proton beam therapy; carbon therapy; heavier ions; clinical trials; charged particle therapy

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Introduction

After observing the depth-dose properties of protons accelerated by the first cyclotrons designed by Ernest Lawrence in the 1930s, Robert Wilson published in 1946 the seminal paper proposing the use of fast protons for radiation therapy in humans (1,2). Shortly thereafter, Lawrence finished building the 184-inch synchrocyclotron in the Berkeley hills at the future site of Lawrence Berkeley National Laboratory. The so-called "Big Machine" was capable of accelerating both protons and helium nuclei to the much higher kinetic energies needed for the depth of penetration required for human treatment. Since the first patient treated at LBNL in 1954 in the U.S. and at Gustav Werner Institute in Uppsala in 1957, protons and other heavier charged particles have been used increasingly to treat a greater variety of cancers and various nonmalignant conditions. Since then, more than 100,000 patients have been treated with charged particle beam therapy, of which 87,000+ are proton and 14,000 are carbon and other heavier ions (3).

Given the ability to focus the radiation dose conformably on an internal target lesion with less dose to surrounding normal tissues, particle-beam therapy has become more prevalently considered as a better radiation treatment option versus photon therapy. The achievable, 3-dimensional dose-precision with charged-particle irradiation benefits patients by improving local control with a more aggressive dose within the target volume and/or by causing less adverse sequelae to adjacent healthy tissues due to the smaller integral dose outside the target volume.

The technology of proton and heavier-ion therapy has improved clinically over the last few decades. As the therapy is relatively novel, however, standards of treatment for different cancers are currently evolving based upon numerous, ongoing clinical studies. Until the recent compilation of particle-beam-therapy protocols, these studies have been published in a wide variety of medical-science journals. By means of this brief summary, we hope to increase physician awareness of the available clinical trials and of the expanding, evidence-based data worldwide in particle-beam therapy.

Methods

The idea of compiling clinical protocols for proton and heavier-ion therapy was introduced and discussed at the Particle Beam Therapy Co-Operative Group (PTCOG)

Table 1 Overview of clinical charged-particle protocols

Parameter	Number of protocols
Particle evaluated	
Carbon	5
Proton	59
Study category	
Randomized	5
Phase I/II	49
Phase III	3
Registry	6
Physics	4
Number of participating centers	
Single institution	58
Multiple institutions	6
Protocols examining combined modalities	21
Recruitment status	
Open	26
Closed	10
Unknown	28

Publication Committee in May 2011. A standard template was then developed to include the following information: title, principle investigator, contact information, additional information, institution, study purpose, accrual information, primary and secondary aims, methods, eligibility, and exclusion criteria. The presented initiative was subsequently approved by the PTCOG Steering Committee.

The collection of clinical trials was accomplished by auditing the National Cancer Institute (NCI) www.clinicaltrials.gov website and through Steering Committee members (4). All radiation treatment protocols found were then individually examined, and the relevant information for all charged-particle studies was entered into the previously developed, formatted templates for tabulation and compilation. Any missing information at participating institutions worldwide was gathered by email inquiry or left blank. All protocols were then organized by treatment site. Subsequently, the compilation was reviewed by PTCOG for accuracy and completeness. Additional protocols will be added as they are initiated.

Results

A total of 64 protocols were compiled from those available on the NCI website, from PTCOG members, and from email inquiries, representing the efforts of ten proton and/or heavier-ion therapy centers. The following tables summarize the compilation overview, list the participating institutions, and highlight the treatment sites and categories currently under investigation for response to charged-particle therapy.

Table 2 Participating centers

Center	Number of protocols
Univ. of Penn. Abramson Cancer Center	22
University of Florida Proton Therapy Institute	20
National Cancer Center of Korea	8
Mass. General Hospital: Francis Burr Proton Center	5
Univ. of Texas MD Anderson Cancer Center	6
Univ. of Heidelberg	3
Loma Linda Univ.	3
Proton Collaborative Group (Chicago, OKC, NJ)	2
Russian Scientific Center of Roentgeno-Radiology	2
St. Jude's Children's Hospital	2

Discussion

Table 1 lists 64 clinical protocols underway in 10 institutions. Proton therapy is being studied in 59 trials and carbon therapy in 5 trials. Multi-modality treatments (chemotherapy and also including X-ray therapy) are evaluated in 21 protocols. The majority are phase I/II studies, but 5 are prospective, randomized trials (three comparing proton versus carbon). Six have multi-center collaboration, and the rest are of single-institution variety. *Table 2* lists the number of clinical trials at each of the 10 centers, and *Table 3* lists them by disease site. The majority of trials are in the prostate [13], pediatric [8], CNS [9] and para-spinal [8] areas, but there are also a good number involving breast [5] and lung [9]. For the breast studies, proton beam therapy is used in boost treatment and also in accelerated partial breast irradiation. For lung studies, proton beam therapy is used in treatment of advanced (stage III) lung cancer and also in early stage (I) as hypofractionation or as stereotactic body radiation therapy. For GI sites, proton beam therapy is used in variety of sites including liver, pancreas, rectum and esophagus.

Conclusions

Despite that more than 100,000 patients have been treated with particle beam over the last 60 years at more than 30 centers around the world, only a small percentage of these patients are treated on clinical trials. As increasing number of particle beam centers are in operation and being developed, the clinical indications for particle beam therapy need to go beyond the traditional uses such as pediatrics, ocular tumors, sarcoma, and base of skull tumors. The compiled list of clinical protocols shows a diversified potential applications in cancers of the lung, head and neck, gastrointestinal

Table 3 Treatment site or category

Type	Number of protocols
Pediatrics	8
Central nervous system (including base of skull)	9
Paraspinal (including sarcoma)	8
Head and neck	4
Thoracic	
Breast	5
Lymphoma	2
Lung	
Stage III	6
Stage I: stereotactic body irradiation	3
Gastrointestinal	
Esophagus	2
Stomach	1
Pancreas	4
Rectum	1
Liver (primary)	2
Liver metastases: stereotactic body irradiation	1
Prostate	
High risk	3
Intermediate and low risk	7
Hypo-fractionated treatment	1
Post-operative treatment	2
Gynecologic: peri-aortic lymph node recurrence	1
Testicular	1
Bladder	1
Other recurrence	2
General registry	3

tract, prostate, breast, brain, gynecologic sites, lymphoma, and recurrent tumors. These clinical trials will validate or invalidate the use of particle beam for these disease sites. The compilation and posting of clinical trials will enhance awareness and accelerate the patient accrual to provide the answers. The other benefit of these listings will be for clinicians who are planning new clinical trials basing on these information, and we hope to promote multi-center collaboration. The authors believe that likely there may be more, now-unreported clinical trials currently underway, and we hope that these centers will recognize our efforts and contribute to this listing.

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Footnote

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