Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 1, pp. 239–246, 2011

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.07.1976

BIOLOGY CONTRIBUTION

RELATIVE BIOLOGICAL EFFECTIVENESS OF CARBON IONS FOR LOCAL TUMOR CONTROL OF A RADIORESISTANT PROSTATE CARCINOMA IN THE RAT

Peter Peschke, Ph.D.,* Christian P. Karger, Ph.D.,† Michael Scholz, Ph.D.,‡ Jürgen Debus, M.D., Ph.D.,§ and Peter E. Huber, M.D., Ph.D.*§

*Clinical Cooperation Unit Radiation Oncology and †Department of Medical Physics in Radiation Oncology, German Cancer Research Center, Heidelberg, Germany; ‡Department of Biophysics, Helmholtz Center for Heavy Ion Research, Darmstadt, Germany; and §Department of Clinical Radiology, University of Heidelberg, Heidelberg, Germany

Purpose: To study the relative biological effectiveness (RBE) of carbon ion beams relative to X-rays for local tumor control in a syngeneic rat prostate tumor (Dunning subline R3327-AT1).
Methods and Materials: A total of 198 animals with tumors in the distal thigh were treated with increasing single and split doses of either ^{12}C ions or photons using a 20-mm spread-out Bragg peak. Endpoints of the study were local control (no tumor recurrence within 300 days) and volumetric changes after irradiation. The resulting values for D_{50} (dose at 50% tumor control probability) were used to determine RBE values.
Results: The D_{50} values for single doses were 32.9 ± 0.9 Gy for ^{12}C ions and 75.7 ± 1.6 Gy for photons. The respective values for split doses were 38.0 ± 2.3 Gy and 90.6 ± 2.3 Gy. The corresponding RBE values were 2.30 ± 0.08 for single and 2.38 ± 0.16 for split doses. The most prominent side effects were dry and moist desquamation of the skin, which disappeared within weeks.
Conclusion: The study confirmed the effectiveness of carbon ion therapy for severely radioresistant tumors. For 1- and 2-fraction photon and ^{12}C ion radiation, we have established individual D_{50} values for local tumor control as well as related RBE values. © 2011 Elsevier Inc.

Carbon ion radiotherapy, Dose–response, Dunning prostate tumor R3327, Local tumor control, Relative biological effectiveness.

INTRODUCTION

Worldwide, the interest in carbon ion radiotherapy is increasing. After pioneering clinical studies at the Lawrence Berkley Laboratory (University of California) for several ion types (1, 2), a clinical research program was initiated at the National Institute of Radiologic Sciences in Chiba, Japan in 1994 (3–8). In 1997, carbon ion radiotherapy started at the Gesellschaft für Schwerionenforschung (Darmstadt, Germany) and reported promising results (9–13).

Carbon ions exhibit an inverted depth–dose profile, which allows for precise irradiation of deep-seated targets (14, 15). In addition to these physical advantages, carbon ions are characterized by an enhanced relative biological effectiveness (RBE), which is higher in the Bragg peak than in the beam entrance region (16). Mechanistically, carbon ions cause clustered DNA damage, which aggravates DNA repair, leading to enhanced cell inactivation, which is assumed to be less dependent on genetic disposition, as well as on oxygen and cell cycle status (17–20).

In carbon ion radiotherapy, dose prescriptions refer to biological effective doses, and for their calculation tissue-specific RBEs have to be assigned to each point. To estimate the RBE for normal and neoplastic tissues at each point, a radiobiological model (21) was integrated into the treatment planning system (TPS). Unfortunately, RBE is a complex quantity, depending on physical parameters such as particle type, dose per fraction, and linear energy transfer (LET), as well as on biological factors like cell or tissue type and the selected biological endpoint. Because the RBE for clinical situations involves rather large uncertainties, biological systems were used to evaluate RBE relationships at various depths and their dependence on dose per fraction. Most of

Reprint requests to: Christian Karger, Ph.D., Department of Medical Physics in Radiation Oncology (E040), German Cancer Research Center, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany. Tel: (+49) 6221-56-38965; Fax: (+49) 6221-56-4631; E-mail: c.karger@dkfz.de

Supported in part by Bundesministerium für Bildung und Forschung (KVSF, 03NUK004A,C, and 06HD156).

P.P. and C.P.K. contributed equally to this work.

Conflict of interest: none.

Acknowledgments—The authors thank Alexandra Tietz and Angela Funk (German Cancer Research Center) and Thilo Elsässer (Gesellschaft für Schwerionenforschung [GSI] Helmholtz Center for Heavy Ion Research) for their excellent technical support; E.W. Hahn for his valuable advice and on-site assistance with study design and setup of the radiation procedure; and GSI for providing excellent experimental conditions with the highly sophisticated beam scanning technique.

our present knowledge about tolerance doses and dose dependence of RBEs was derived from experiments with mouse skin (22) and jejunum (23), as well as from rat brain and spinal cord (24–27). Carbon ion effects in experimental solid tumors are addressed by only a few studies using human tumor cell line xenotransplants or syngeneic mouse models with tumor growth inhibition as biological endpoint (28–31).

The present study investigates the response of well-characterized tumor sublines to carbon ion therapy. We have selected a syngeneic tumor system consisting of several cell lines, which represent the spectrum of androgen responsiveness, tumorigenicity, and metastatic ability seen during the progression of human prostate cancer (32). Growth delay and the probability of local tumor control in relation to locoregional side effects were selected as clinically significant biological endpoints.

METHODS AND MATERIALS

Tumor model

The anaplastic subline AT1 of the Dunning prostate adenocarcinoma R3327 was subcutaneously implanted in the distal thigh of young adult male Copenhagen rats (180 g). This syngenic tumor is considered an excellent model system for human prostate tumor and has been extensively characterized in terms of ultrastructure, hormones, response to therapy, and immunogenicity (33). Tumor material was kept identical for all experiments by transplanting fresh tissue from tumors grown from a cryopreserved stock, maintained as a first passage of the original tumor tissue kindly supplied to us by J. T. Isaacs (Johns Hopkins University, Baltimore, MD). Ploidy status, histology, and the growth rate of control tumors were determined as measures of quality assurance. All experiments were approved by the governmental review committee on animal care, and animals were kept under standard laboratory conditions at the German Cancer Research Center. During all irradiation procedures, rats were deeply anesthetized by i.p. injection of Ketaminehydrochloride (125 mg/kg) mixed with Xylazinehydrochloride (20 mg/kg).

Experimental setup

Average diameter of the tumors before treatment was 9 mm (range, 7.0–10.5 mm). Tumors larger than 10.5 mm in one direction were excluded from the study. Irradiations were performed with a single horizontal beam that hit the tumor from the rear direction. Rats were placed on a specially designed device allowing for rigid and reproducible fixation of the tumor relative to a milled marker on the device (Fig. 1a and b), and the device was aligned on the treatment table with crossed laser beams. In a setup experiment, the

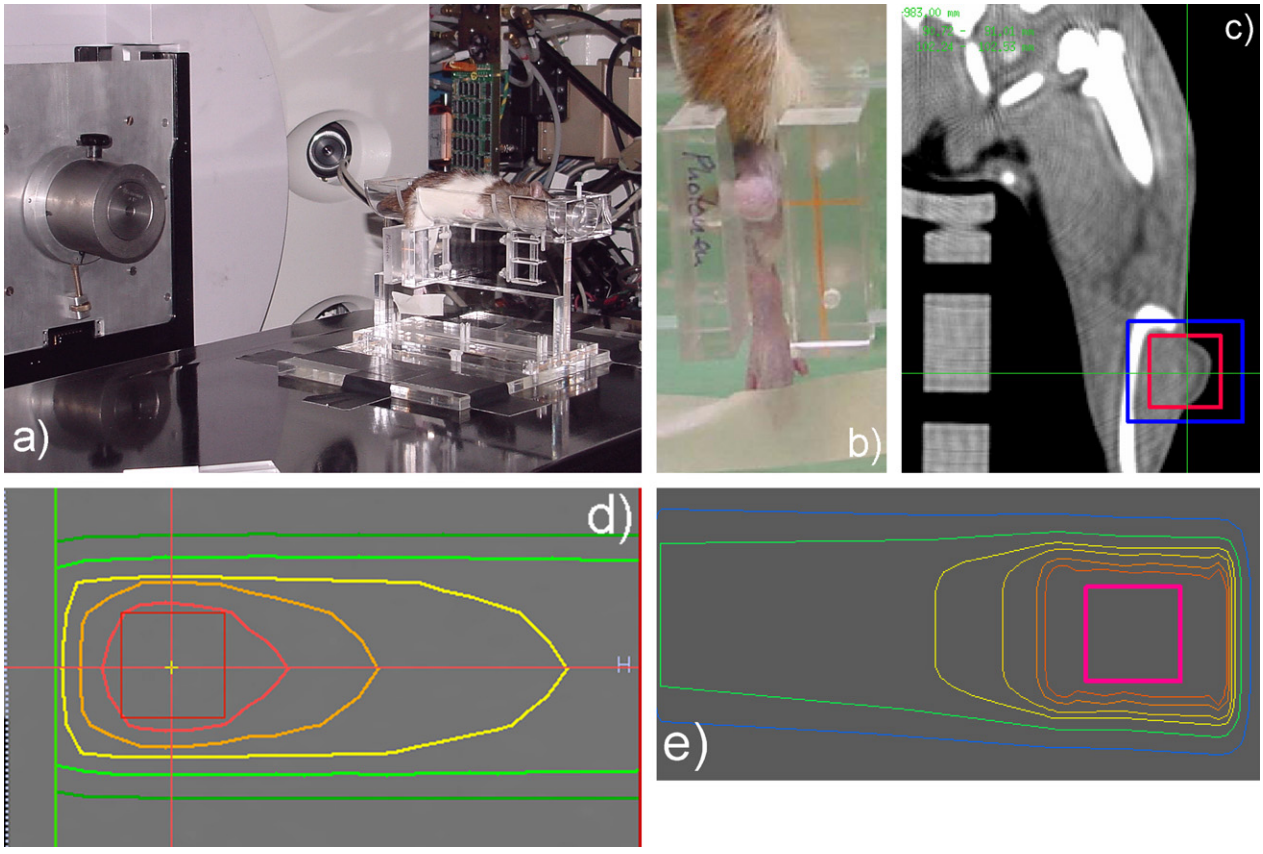

Fig. 1. (a) Setup of the immobilization device for irradiation (here for photons) for the local treatment of s.c. growing tumors (b). Irradation was performed horizontally from the rear direction. (c) The clinical target volume (red) was extended horizontally by a 3-mm and vertically by a 2-mm margin to obtain the planning target volume (PTV) (blue). The resulting PTV extension was 16 × 14 mm^2. (d, e) Sagittal views of the dose distributions in water together with the clinical target volume (PTV not shown) for (d) photons (95%, 90%, 80%, 50%, and 20% isodoses) and (e) carbon ions (95%, 90%, 80%, 70%, 50%, and 20%).