High tolerance of the rat spinal cord to microplanar irradiation

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Rationale and objectives

Several radio-oncologists familiar with animal studies of microbeam radiation therapy (MRT) have suggested that this technique might enable the palliation of central nervous system malignancies in infants and young children that cannot, at present, be safely palliated by existing radiation therapies[1]. The main objective of the present study was to determine the radiation dose required to induce delayed foreleg myeloparesis in 50% of initially normal rats (ED_{50}) following multiple transverse irradiations of an ~1 cm-long segment of their cervico-thoracic spinal cords.

Methods

Microplanar irradiation: The segment including C6 to T2 of the spinal cord of anesthetized, prone, young adult male rats (SPF Fischer, body weight 220-260g) was irradiated at the MRT facility of ID 17 (ESRF, Grenoble) laterally, anatomically from right to left, by a ~10.6 mm-wide array consisting of 52 microplanar beams ~35 μm-wide, 20 mm-high, spaced at ~210 μm intervals. The entrance doses were approximately 330, 470, 660, and ~940 Gy. There were 8 to 10 rats per dose group; 4 rats were sham-irradiated controls.

Seamless synchrotron X-ray beam: Young female rats were also irradiated with synchrotron X rays, in the same facility, in the same prone position, but by a seamless collimated beam, 1.35 mm-wide and 2.5 cm-high, with a 16 mm-thick Al filtration. The antero-lateral border of the radiation field was marked by a vertical line drawn through a virtual point situated at ~2 cm posteriorly to the incisura intertragica. The entrance doses were approximately: 80, 160, 200, 250, 310 and 620 Gy.

The rats were closely monitored for impaired foreleg function by a colleague (DD) experienced in animal husbandry. Rats displaying signs of paresis/paralysis of both forelegs were killed using a standard regulated procedure. All remaining other rats were killed ~1 year after irradiation and the cervico-thoracic spinal cords processed for histopathology.

Results

Paralysis was accompanied by a loss in body weight in the 940 Gy and 660 Gy dose groups (microplanar irradiation) , with all rats in these two subgroups killed by day 56 and

day 60 after irradiation, respectively. With the exception of two rats in the 470 Gy dose group that had to be killed at 289 and 311 days (~41 and ~44 weeks) after irradiation, none of those and none in the ~330 Gy group ever showed foreleg dysfunction. In the latter two groups changes in body weight were similar to those of control rats. After synchrotron X-ray irradiation in the seamless mode, no rat survived without paralysis beyond 2, 3, 11 or 156 days (~22 weeks) after entrance doses of ~620, 310, 250 or 200 Gy, respectively.
Sagittal histological sections of the spinal cord of rats killed from 52 to 311 days after microplanar irradiation displayed areas of white matter necrosis, often associated with fibrinoid vascular necrosis, all within the microbeam array. The striped microplanar irradiation paths were roughly 40 μm wide, separated by on-center distances of ~190 μm.

Conclusions

A rough preliminary visual interpolation of the data yielded an entrance dose ED_{50} of ~530 Gy for foreleg paralysis after 52 simultaneous parallel microplanar synchrotron X-ray beam irradiations (MRT) over an ~10.6 mm-long cervico-thoracic cord segment, about three times the entrance dose ED_{50}, ~180 Gy after one 1.35 mm-wide seamless synchrotron X-ray beam irradiation. Conversely, seamless or broad-beam irradiation of an 8 mm-long cervical cord segment with a single dose of 250kV X- rays yielded an entrance dose ED_{50} of ~30 Gy in >30 weeks; the ED_{50} increased to ~51 Gy when the irradiated segment was only 4 mm-long [2].

Marked histopathologic lesions have been found in the spinal cord of all rats irradiated using the MRT mode and killed following the development of clinical signs of paralysis. The presence of conspicuous vascular lesions such as necrosis, recent and older hemorrhage, involving not only tissue slices irradiated with peak doses, is compatible with the notion of a primarily endothelial pathogenesis of central nervous system (CNS) damage caused by ionizing radiation that may result in a CNS radiation syndrome [3], or in white matter necrosis [4]. The post-irradiation latency of clinical signs was ~ 8 weeks for both high dose groups, i.e., 940 and 660 Gy, and ~ 10 months for two rats in the 470 Gy subgroup. This indicates the need for caution against the early assessment of radiation damage or its absence, particularly in the CNS. Thus, no damage was observed to the brain vasculature within one month after a 1000 Gy entrance irradiation dose using the MRT mode [4]. Dilmanian et al [5] exposed the spinal cord of few rats, transversely, to 400 Gy from four 0.68 mm-wide microbeams, spaced 4 mm apart on center. None of these rats showed paralysis or behavioral changes during their 7 month observation period.
The dose delivered to tissue slices between the microplanar beams, the “valley dose”, is likely to be of prime importance for the extent of tissue damage, as a spatially fractionated array should biologically result in a broad beam effect when the valley dose exceeds threshold values for normal tissue damage. Conceivably, the valley dose might also alter the ED50 of the peak dose.
The reasons for the remarkable relative tolerance of the CNS for MRT-type irradiations may be related to a small-volume effect due to the presence of a huge interface between highly irradiated tissue slices and underirradiated interjacent contiguous tissues. Even four spatially fractionated macroscopic “minibeams”, 0.68 mm thick, widely (1.36 mm) spaced on center, with an entrance dose of 170 Gy, impacting transversely on a normal rat spinal cord, may be tolerated for 7 months[5]. Such findings suggest potential applicabilities of microbeams – and/or perhaps of minibeams – to clinical palliation of tumors.

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