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BIOLOGY CONTRIBUTION

COMPATIBILITY OF THE LINEAR-QUADRATIC FORMALISM AND BIOLOGICALLY EFFECTIVE DOSE CONCEPT TO HIGH-DOSE-PER-FRACTION IRRADIATION IN A MURINE TUMOR

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Purpose: To evaluate the compliance of linear-quadratic (LQ) model calculations in the high-dose range as used in stereotactic irradiation in a murine tumor model.

Methods and Materials: Female 10-week-old Balb/c mice bearing 1-cm-diameter EMT6 tumors in the hind legs were used. Single doses of 10–25 Gy were compared with 2–5 fractions of 4–13 Gy given at 4-hour intervals. Cell survival after irradiation was determined by an *in vivo–in vitro* assay. Using an α/β ratio determined for *in vitro* EMT6 cells and the LQ formalism, equivalent single doses for the hypofractionated doses were calculated. They were then compared with actually measured equivalent single doses for the hypofractionated doses. These fractionation schedules were also compared simultaneously to investigate the concordance/divergence of dose–survival curves plotted against actual radiation doses and biologically effective doses (BED).

Results: Equivalent single doses for hypofractionated doses calculated from LQ formalism were lower than actually measured doses by 21%–31% in the 2- or 3-fraction experiments and by 27%–42% in the 4- or 5-fraction experiments. The differences were all significant. When a higher α/β ratio was assumed, the discrepancy became smaller. In direct comparison of the 2- to 5-fraction schedules, respective dose–response curves almost overlapped when cell survival was plotted against actual radiation doses. However, the curves tended to shift downward by increasing the fraction number when cell survival was plotted against BED calculated using an α/β ratio of 3.5 Gy for *in vitro* EMT6 cells.

Conclusion: Conversion of hypofractionated radiation doses to single doses using the LQ formalism underestimated the *in vivo* effect of hypofractionated radiation by approximately 20%–40%. The discrepancy appeared to be larger than that seen in the previous *in vitro* study and tended to increase with the fraction number. BED appeared to be an unreliable measure of tumor response. © 2011 Elsevier Inc.

Linear-quadratic model, Biologically effective dose, Stereotactic radiosurgery, Stereotactic radiotherapy, Murine tumor.

INTRODUCTION

With improvements in radiotherapy machines and techniques, stereotactic irradiation (STI) is increasingly common worldwide. Single-fraction stereotactic radiosurgery is now widely used for relatively small brain metastases, and stereotactic radiotherapy using 3–5 fractions is employed for larger brain metastases and relatively small primary or metastatic tumors of the lung and liver (1–3). Clinical evidence is gradually accumulating with respect to appropriate doses and fractions, but optimal schedules still need to be determined in many tumors in future studies. To compare fractionation schedules and evaluate the effect of fractionated irradiation, the linear-quadratic (LQ) formalism and biologically effective dose (BED) derived from the LQ model (4, 5) are often used because of their convenience and simplicity. Although the LQ formalism is useful for conversion between relatively low radiation doses used in conventional radiotherapy, it has been suggested that it is not applicable to higher daily doses or smaller fraction numbers (5–7). However, many clinicians have used the formalism to convert

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hypofractionated doses to single doses in their publications (8, 9), and many have used BED in evaluating the doses of STI (3, 10). To complicate the issue further, some investigators, in contrast, claim that the LQ model is applicable to STI (11, 12). Therefore, it seems necessary to evaluate the applicability of the LQ formalism in single-fraction and hypofractionated radiation schedules.

A recent study in our laboratory compared the effects of single-fraction and hypofractionated irradiation in cells and multicellular spheroids in culture; equivalent single doses for the hypofractionated doses were calculated using the LQ formalism and they were also determined from the cell survival curves (13). There was a non-negligible discrepancy between equivalent single doses calculated by the LQ formalism and those actually measured. The LQ formalism seemed to underestimate the effects of hypofractionated irradiation. In addition, similar but slightly greater tendencies were observed in spheroids (13). Although the LQ formalism should essentially be applied to normal tissues, many investigators use the formalism and BED10 (BED with an α/β ratio of 10 Gy) for tumor responses to fractionated STI (3, 10). Because *in vivo* tumors are quite different from single cells in culture and spheroids in radiation response, it was considered necessary to evaluate the reliability of the LQ formalism in dose ranges as used in STI using *in vivo* tumors. Thus, we examined compatibility of the LQ formalism to single-fraction and hypofractionation radiation schedules in murine tumors in our study.

METHODS AND MATERIALS

Cell line and mouse

EMT6 (murine mammary sarcoma) cell line cultured in Eagle's minimum essential medium supplemented with 12.5% fetal bovine serum was used. Characteristics of the cell line have been described in detail previously (14, 15). Injected subcutaneously into bilateral hind legs of female 8-week-old Balb/c mice were 2×10^5 exponentially growing EMT6 cells. When the tumors grew to about 1 cm in diameter after 12 days, experiments were carried out. Four tumors from two mice were used for each determination.

Irradiation

A 210-kVp X-ray machine (10 mA with 2-mm Al filter) was used to irradiate the cells and tumor-bearing mice. The dose rate was 2 Gy/min. EMT6 single cells and tumor-bearing mice were irradiated using methods described previously (16, 17). The mice received whole-body irradiation without physical restraint or anesthesia because both procedures can artificially increase the hypoxic fraction in tumor (18).

To estimate the α/β ratio of the cell line *in vitro*, appropriate numbers of the cells were plated onto culture dishes and irradiated at 2–12 Gy, as described previously (13). In tumor-bearing mice, single doses of 10, 15, 17.5, 20, 22.5, and 25 Gy were first compared with 2 fractions of 9, 11, and 13 Gy and 3 fractions of 7, 8, and 9 Gy. Then, 4 fractions of 5, 6, and 7 Gy and 5 fractions of 4, 5, and 6 Gy were also compared with the same single doses. According to the results of previous studies showing that sublethal damage repair (SLDR) is completed within 4 hours in this cell line (16), an interfraction interval of 4 hours was used throughout the study.

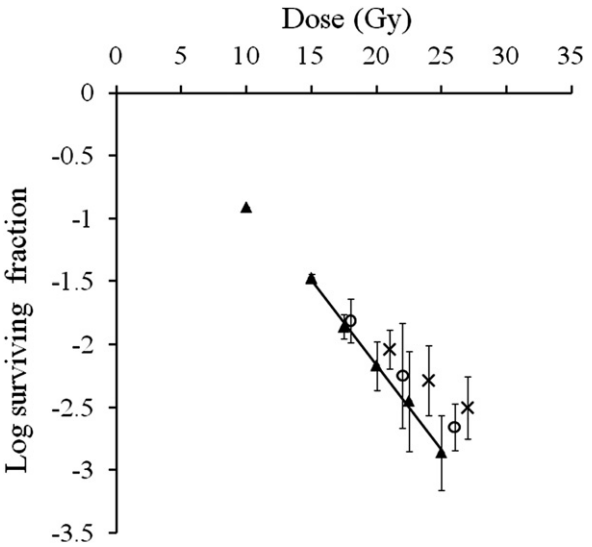

Fig. 1. Surviving fractions of EMT6 cells in Balb/c mice after single- (▼), 2-fraction (○), or 3-fraction (×) irradiation. Bars represent standard deviation (sorry for our mistake) of five experiments.

Cell survival assay

In vitro cell survival was determined by a colony formation assay as described previously (16). Surviving fractions of tumor cells irradiated *in vivo* were determined by an *in vivo–in vitro* assay as described previously (17, 19). Briefly, excised tumors were minced and treated with 0.25% trypsin and 0.02% ethylenediaminetetraacetic acid at 37°C for 30 min. Then viable cell numbers were counted, and adequate numbers of cells were plated onto dishes with the culture medium described earlier. After 9 days, colonies were fixed with 70% ethanol and stained with Giemsa. Colonies containing more than 50 cells were counted.

Linear lines were fitted to high-dose (≥15 Gy) regions of dose–survival curves for the single-fraction group and an approximation equation was obtained. Single doses equivalent to the hypofractionated radiation doses were then estimated from the equation (measured dose).

Dose–survival data for cultured EMT6 single cells were fitted by the LQ formalism and an α/β ratio for EMT6 was calculated. Using the α/β ratio and the LQ formalism, equivalent single doses for the hypofractionated doses were calculated (calculated dose). Then the measured and calculated equivalent single doses were compared in a way similar to that used in our previous *in vitro* study (13). The Mann–Whitney *U* test was used to examine the difference between calculated and measured single doses.

Finally, 2- to 5-fraction radiation schedules were compared simultaneously to investigate the discrepancy between dose–response curves according to actual radiation doses and those according to BED determined by the LQ formalism. At 18–24 hours after the start of irradiation, *in vivo–in vitro* assay was performed, and tumor cell survival curves for various fractionation schedules were obtained.

RESULTS

Experiments for drawing a dose–survival curve for EMT6 single cells *in vitro* were performed 5 times, and the α/β ratio was determined each time. From these *in vitro* experiments,

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