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THE RBE OF FAST NEUTRONS FOR IN VITRO INACTIVATION OF HUMAN TUMOUR CELLS DETERMINED BY THE RATIO OF MEAN INACTIVATION DOSES

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In an effort to clarify the relationship between sensitivity of human tumour cells to low-LET and to fast neutron irradiation, 10 human tumour cell lines were exposed to cobalt gamma-rays and to 60 MeV ($p \rightarrow Be^+$) neutron beam. The data were pooled with results of 31 human tumour cell lines previously published. The analysis of data using the linear-quadratic model indicated that not only α values increased after neutron irradiation, but so did β values too, although to a lesser extent. The mean inactivation dose (MID) was derived for each cell line from the linear-quadratic parameters after low-LET and high-LET exposure. MID values following neutron irradiation were closely correlated to those after gamma-ray irradiation. In these 41 cell lines, the extreme values of RBE derived by the ratio of MID varied by a factor of 3 among the cell lines. RBE was positively correlated to photon MID, meaning that intrinsically radiation resistant tumour cells have a higher neutron RBE, on average. Similar findings were observed if α ratios were used instead of MID ratios. In addition, the RBE/dose variations were more marked in cells with the higher RBE. Taken together, these data suggest that, although considerable variations exist among human tumour cell lines, intrinsically radioresistant cells are relatively more sensitized when exposed to high LET beams than radioresponsive tumours. An 'intrinsic gain factor' may thus be expected in irradiating radiation resistant tumours with fast neutrons, in addition to the hypoxic or kinetic gain factors. Because the quadratic component is still present after neutron irradiation, we suggest using MID ratio as a reference RBE when comparing survival curves of cells exposed to radiations of different qualities.

High LET beams such as fast neutrons may provide a therapeutic gain in tumours with a high amount of hypoxia or poor reoxygenation, and in tumours which contain a substantial proportion of non-cycling cells or cells in resistant phases of the cell cycle (1, 2). Moreover, and because single hit damage plays an important role in cell kill after neutron irradiation, it has been stated that cells resistant to photon irradiation because of necessity of interaction of 2 hits for lethality or because of proficient repair, would be preferentially killed with neutrons (3, 4). Therefore, the intrinsic radioresistance of a tumour cell to photons has been suggested to be a factor for selection of neutron treatment (2, 5).

Experimental evidence to ascertain this proposal has been inconclusive due to either a few number of tumour cells to be studied (6) or to the choice of the parameter to compare response to low- and high-LET radiation. Survival to 2 Gy of photons has been compared to survival to different doses of neutrons (7). Although clinically useful this procedure yielded variable results, depending on the neutron dose. An appropriate analysis is to find out whether the RBE varies with the intrinsic sensitivity to photons. Because RBE changes with dose (or survival) the

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Table 1

Histology, ploidy and radiation response parameters of 10 human tumour cell lines

Cell line	Histology	DNA index	Photons			Neutrons		
			Alpha (Gy^{-1})	Beta (Gy^{-2})	MID* (Gy)	Alpha (Gy^{-1})	Beta (Gy^{-2})	MID* (Gy)
CAL4	Skin melanoma	1.44	0.118 (0.01)	0.047 (0.003)	3.09 (0.10)	0.431 (0.072)	0.164 (0.037)	1.32 (0.02)
CAL7	Skin melanoma	1.70	0.259 (0.035)	0.033 (0.003)	2.56 (0.14)	0.828 (0.065)	0.036 (0.011)	1.11 (0.05)
CAL12	Squamous carcinoma tongue	1.24	0.151 (0.006)	0.041 (0.001)	3.07 (0.11)	0.332 (0.063)	0.119 (0.009)	1.61 (0.09)
CAL27	Squamous carcinoma tongue	1.01	0.186 (0.012)	0.051 (0.002)	2.60 (0.06)	0.545 (0.049)	0.109 (0.006)	1.30 (0.05)
CAL51	Breast adenocarcinoma	1.00	0.354 (0.045)	0.030 (0.002)	2.17 (0.16)	0.577 (0.108)	0.099 (0.018)	1.28 (0.11)
CAL54	Renal adenocarcinoma	1.43	0.355 (0.034)	0.045 (0.001)	2.00 (0.11)	0.440 (0.010)	0.123 (0.021)	1.41 (0.09)
CAL58	Glioblastoma	1.45	0.188 (0.031)	0.047 (0.005)	2.67 (0.09)	0.459 (0.072)	0.117 (0.02)	1.40 (0.06)
CAL62	Thyroid carcinoma	1.46	0.164 (0.011)	0.072 (0.008)	2.42 (0.05)	0.341 (0.053)	0.184 (0.024)	1.39 (0.02)
CAL110	Ewing sarcoma	1.88	0.784 (0.048)	0.011 (0.007)	1.24 (0.05)	1.702 (0.096)	0 (0)	0.59 (0.03)
CHP100	Neuroblastoma	1.73	0 (0)	0.155 (0.009)	2.26 (0.07)	0.553 (0.092)	0.241 (0.029)	1.06 (0.05)

* Mean inactivation dose; Standard errors between parentheses.

RBE at a certain dose level is not valid for other dose levels (1, 8). RBEs determined by α ratios (α neutrons/α photons) concern very low doses and are more relevant to radioprotection. Alternatively, RBE estimated by ratio of D_0 are influenced by the terminal portion of the survival curve; moreover D_0 may not be the most suitable parameter to describe the survival curve and to fit the experimental points (9). A convenient single parameter that describes overall sensitivity is the mean inactivation dose (MID) (10, 11). Its use carries many advantages: 1) it represents the radiosensitivity of the cell population as a whole; 2) it predicts radiosensitivity among histological groups better than any other parameter (12); 3) it has a low coefficient of variation (12–14); 4) it has units of dose (Gy); 5) it is strongly influenced by survival at clinically relevant doses; and 6) its use is recommended by the ICRU (15). For these reasons, the ratio MID photons/MID neutrons would be an appropriate definition of the RBE of a high LET beam. With this entity we have attempted to investigate whether radioresistant tumour cells have a higher RBE to fast neutrons than radiosensitive tumour cells. Experiments were conducted on 10 human tumour cell lines and the results were added to 31 human tumour cell lines previously reported (6, 16), where the LQ parameters allowed to compute the MID. We thought findings based on 41 cell lines would carry less errors than those based on a fewer number of cells. Non-neoplastic cells were excluded in order to focus on tumour cells, and to avoid extreme values of sensitivity such as in ataxia telangiectasia cells, which may distort the distribution (16).

Material and Methods

Cell lines. The origins of the 10 human tumour cell lines are shown in Table 1. Except fot CHP100 (17) they were established in our institute from patients undergoing surgical procedures. Other characteristics of these cell lines were reported elsewhere (18–22). All cell lines were grown as monolayers in Dulbecco's modified minimum essential medium to which was added 1% sodium pyruvate (100 mM), 1% L-glutamine (200 mM), 50 IU/ml penicillin, 50 μg/ml streptomycin, and 10% (for cell maintenance) or 20% (for experiments) of heat-inactivated foetal bovine serum (Dutscher). Cells were kept at 37°C in a humidified atmosphere, containing 5% CO_2.

Irradiation conditions. Exponentially growing cells were harvested and appropriate dilutions were plated in culture flasks (Falcon) and allowed to settle in the incubator. Photon irradiation was carried out using a cobalt unit, having a dose rate of 2.05 Gy/min. Neutron irradiation was effected with the biomedical cyclotron Medicyc, producing 60 MeV ($p \rightarrow Be^+$) neutrons, at a dose rate of 0.22 Gy/min. The cells were exposed in the maximum build-up region: 0.5 cm for the cobalt gamma-rays and 2.5 cm for fast neutrons. After irradiation, the flasks were put back in the incubator for 11 to 21 days before colony

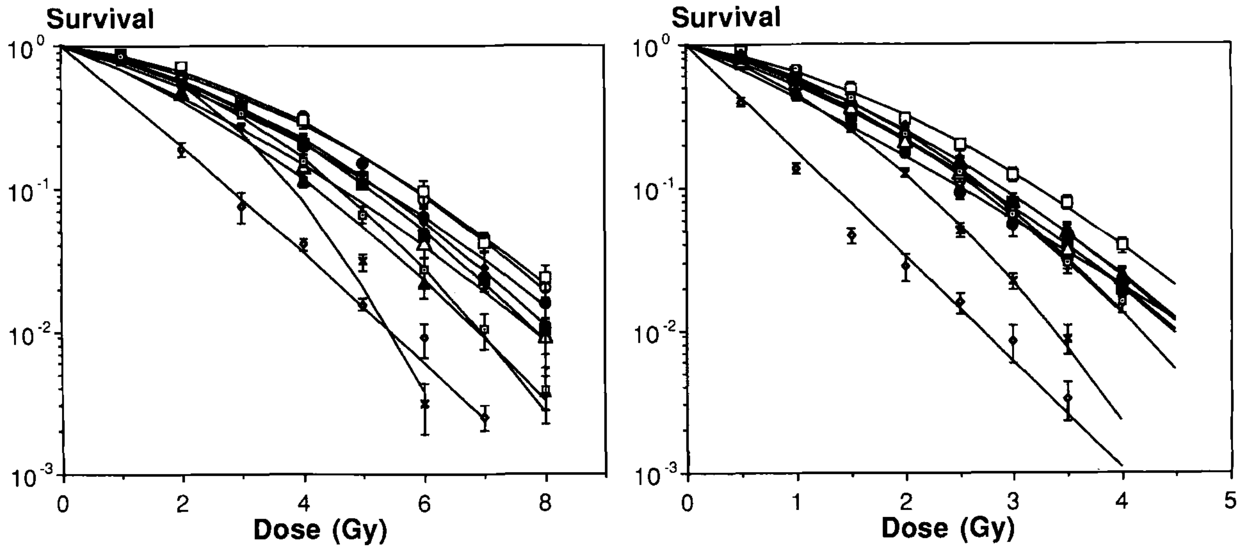

Fig. 1. Survival curves of 10 human tumour cell lines exposed to gamma-rays (left) and to 60 MeV ($p \rightarrow Be^+$) neutrons (right), fitted by the linear-quadratic model. (○) CAL4, (●) CAL7, (□) CAL12, (■)CAL27, (△) CAL51, (▲) CAL 54, (◆) CAL58, (⊡) CAL62, (×) CHP100, (◇) CAL110.

counting. Three to four experiments were carried out for each cell line.

Analysis. Survival curves were fitted using the LQ model and the parameters α, and β and the mean inactivation dose (MID) were derived. MID values were also derived from the reported LQ parameters after photon and neutron irradiation of 5 (6) and 26 (16) human tumour cell lines. Non-neoplastic cell lines were excluded and the results of the 41 cell lines were pooled together. RBE was calculated by dividing photon MID over neutron MID. The RBE at 0.1 survival was also computed as well as the ratio of the initial slopes α. Using the LQ fit, the RBE variation between 2 and 8 Gy gamma-ray dose was investigated. It was calculated with the following equation:

$$\text{RBE variation between 2 Gy and 8 Gy} = \left(1 - \frac{\text{RBE at 2 Gy}}{\text{RBE at 8 Gy}}\right) \times 100$$

A negative value means a reduction of RBE with increase in dose, and a positive value means an increase in RBE with dose. Mean values were compared with Student's t-test, and correlations between variables were assessed with linear regression.

Results

The radiation response of the 10 human tumour cell lines to cobalt gamma-rays and to fast neutrons is illustrated in Fig. 1 and the radiosensitivity parameters are shown in Table 1. The Ewing tumour CAL110 was the most sensitive, and the neuroblastoma CHP 100 was characterized by a sharp bending. These properties were retained following neutron irradiation. The radiation response parameters of the 41 cell lines to gamma-rays and to neutrons is shown in Table 2. The α and β values were negatively correlated after photon irradiation ($r = 0.36$; $p = 0.02$), and more markedly after neutron irradiation ($r = 0.63$; $p < 10^{-6}$). The mean and median RBE as defined by ratio of $MID = 2.15$ and 2.04 respectively (range: 1.31–3.90). It is interesting to note that β values after neutron irradiation were significantly higher than

Table 2

Radiosensitivity parameters and RBEs of the 41 human tumour cell lines

Photons			Neutrons			RBE		
Alpha (Gy^{-1})	Beta (Gy^{-2})	MID* (Gy)	Alpha (Gy^{-1})	Beta (Gy^{-2})	MID* (Gy)	MID* ratio	$D_{0.1\,s}$** ratio	Alpha ratio
0.320	0.045	2.33	0.824	0.080	1.12	2.15	2.03	2.94
(0.035)	(0.005)	(0.10)	(0.066)	(0.009)	(0.05)	(0.09)	(0.07)	(0.24)

* Mean inactivation dose; **Dose for 10% survival; Standard errors between parentheses.

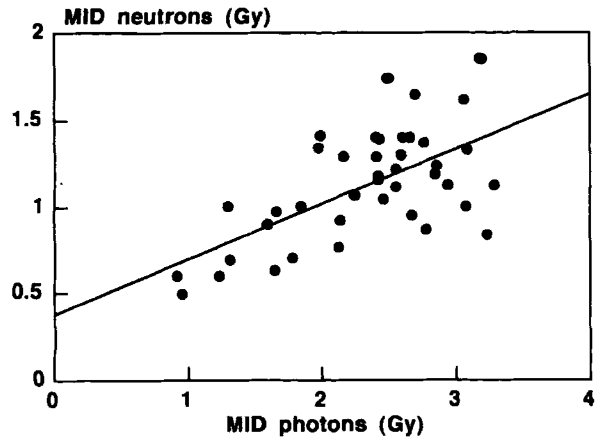

Fig. 2. The relationship of the mean inactivation dose (MID) following fast neutron irradiation to the MID after low LET irradiation in 41 human tumour cell lines. $p < 10^{-5}$

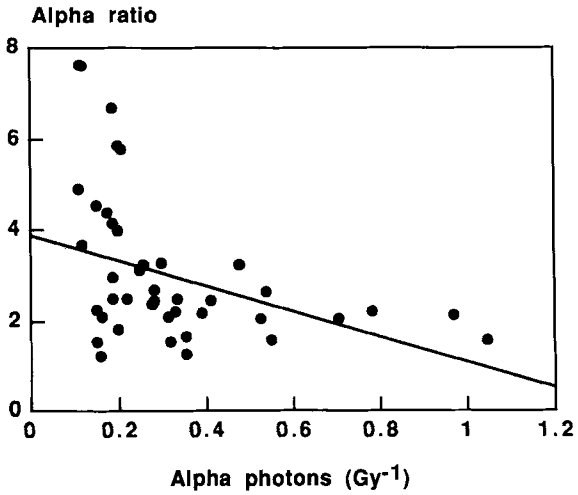

Fig. 4. The RBE determined by the ratio α neutrons/α photons as a function of the intrinsic radiosensitivity to photons measured by α, in 41 human tumour cell lines. $p = 0.008$.

those after gamma-ray irradiation ($p < 10^{-5}$, paired Student's t-test).

The contribution of cell kill due to the quadratic parameter β relative to the total cell kill was calculated for each of the 41 cell lines at clinically relevant doses.

$$\text{This contribution} = \frac{d}{(\alpha/\beta) + d} \times 100$$

At a dose of 2 Gy, this contribution = 26.0 ± 3.1% after photon irradiation and 19.3 ± 2.5% after neutron irradiation, the difference being not significant ($p = 0.10$). However, at a neutron dose of 1.7 Gy which is commonly used in practice, this value was only 17.3 ± 2.3%, which was significantly less than after photon irradiation ($p = 0.027$).

The relation of neutron radiosensitivity to photon radiosensitivity is shown in Fig. 2. The MID after neutron irradiation was significantly correlated to that after low LET irradiation ($r = 0.62$; $p < 10^{-5}$) and so were the α values and the β values (respectively $r = 0.78$; $p < 10^{-6}$ and $r = 0.65$; $p < 10^{-6}$, figures not shown), meaning that cell lines resistant to photon irradiation are also resistant to fast neutron irradiation. However, despite this relation, it was found that the RBE values as defined by MID ratios were higher in radioresistant cell lines. This is depicted in Fig. 3 where a positive correlation was observed between RBE and photon MID ($r = 0.45$; $p = 0.003$). Similarly, α ratios were negatively correlated to photon α ($r = 0.41$; $p = 0.008$, Fig. 4).

Out of the 41 cell lines analysed, 34 showed a reduction of RBE with increase in dose (negative RBE variation). The amplitude of this variation was related to variation in the initial slopes of the photon and neutron radiation survival curves. This is best represented in Fig. 5, where RBE variation was found to be strongly correlated to low

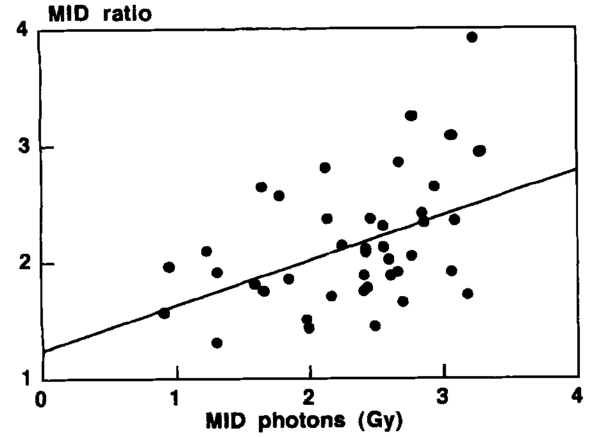

Fig. 3. The RBE determined by the ratio MID photons/MID neutrons as a function of the intrinsic radiosensitivity to photons measured by MID, in 41 human tumour cell lines. $p = 0.003$.

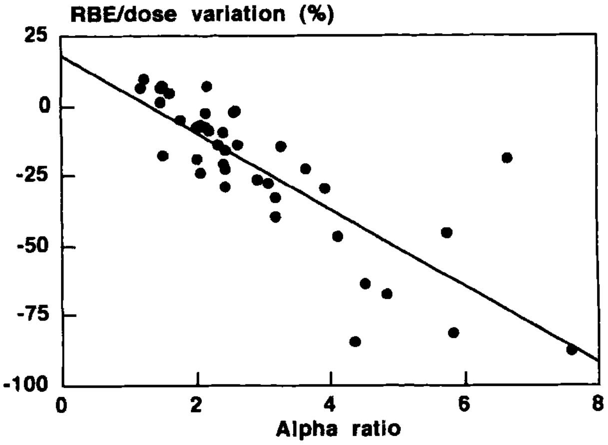

Fig. 5. The RBE variation between 2 Gy and 8 Gy of photons as a function of the RBE measured by α neutrons/α photons. $p < 10^{-6}$.

dose RBE, as determined by α ratio: the higher the α ratio, the greater the reduction of RBE with increase in dose ($r = 0.81$; $p < 10^{-6}$). Similarly, a positive correlation was found between RBE variation and α ($r = 0.39$; $p = 0.011$), α/β ($r = 0.36$; $p = 0.022$), and a negative correlation with β ($r = 0.34$; $p = 0.033$) and with MID ratio ($r = 0.49$; $p = 0.001$) (figures not shown).

Discussion

The pooled results of the 41 human tumour cell lines analyzed in this study shed further light on the relation between radiation response to low LET and to high LET radiation. Although there were some energy differences in the 3 sets of neutron versus photon data: 50 MeV p → Be neutrons versus Cs γ-rays (6), 62.5 MeV p → Be neutrons versus 4 MeV photons (16) and 60 MeV p → Be neutrons versus Co γ-rays (Table 1), the spread of data in each set has necessitated pooling in order to increase the experimental power. Indeed, some RBE variations may arise due to these differences in beam qualities but they are likely to be mild. For instance, the higher effectiveness of Cs γ-rays relative to Co γ-rays is compensated by a higher effectiveness of the 50 MeV p → Be neutron beam relative to the 60 MeV p → Be neutron beam.

As expected, radiation response to fast neutrons is mainly characterized by an increase in the linear term α, indicating an increase in lethality due to single track events. The ratio of α after neutron irradiation to α after gamma-ray irradiation can be considered as the maximum RBE; its average value = 2.94, but individual values cover a range from 1.19 to 7.61. In addition to increase in α there was an increase in the quadratic term β. The increase in β was less than that in α, and although β values may not be estimated with accuracy when associated with high α values (23), the increase in β was highly significant: $p < 10^{-5}$, not predicted by theories stipulating that β is independent of LET (24–26). An increase in β with increase in LET has been previously reported (27–30). If the quadratic term represents lethality due to interaction of 2 DSB induced by 2 independent particles, the RBE of this kind of lethality can be derived by calculating $\sqrt{\beta}$ neutrons/$\sqrt{\beta}$ photons (27). In this series, this RBE = 1.32 ± 0.09. Although it is almost half the α ratio, it is significantly higher than 1. Doses per fraction of 1.70 Gy are commonly used in neutrontherapy (31, 32). With this fractionation, cell kill due to the quadratic component is not negligible: about 17% of the total cell kill versus 26% after a dose per fraction of 2 Gy of photons. For this reason, the use of MID appears more appropriate than α in defining the intrinsic radiosensitivity as well as for RBE measurements.

Radiosensitivity to photons is correlated to radiosensitivity to neutrons (Fig. 2). Despite this correlation, the RBE is related to low LET response. Whether MID ratios (Fig. 3) or α ratios (Fig. 4) are used, these findings as well as other observations on non-neoplastic cells exposed to high LET radiation (33, 34) indicate that radiosensitive cells have lower RBE than radioresistant cells. To the extent that in vitro survival data reflect the in vivo radiation response (35, 36), these findings comfort the clinical impression that a gain factor is likely to be achieved for resistant tumours following high LET radiation. This 'intrinsic gain factor' is to be added to the well-known hypoxic and kinetic gain factors that form the rationale for using high LET radiation in radiotherapy.

With regard to RBE variation with dose, the greater increase in α (than in β) after high LET radiation makes RBE increase with the decrease in dose and vice versa. In the 41 cell lines studied, although the median drop of RBE was 18% when the photon dose increased from 2 to 8 Gy, the range varied from 88% decrease to 9% increase. An increase in RBE, albeit mild, with increase in dose has been observed in 7 cell lines, which showed most increase in β after neutron irradiation. These findings suggest that, in addition to RBE variations among tumour cells, the variation of this RBE according to fractionation is another factor to be considered. The sharpest drop of RBE with increase in dose was encountered in tumour cells with the highest RBE (Fig. 5), which are the most resistant cells, and those with low α/β ratio, as we have previously observed after charged particles irradiation (37). This is due to the particular shape of the photon survival curve, and it recalls the reasons of the increase in RBE at low dose per fraction for late effects, which are characterized by low α/β ratios (38).

Finally, we suggest the use of the ratio of MID to derive a single RBE value when survival curves to low- and high-LET radiation are to be compared. This value could be taken as the reference RBE. With this parameter it is shown that, despite a 3-fold variation of neutron RBE among human tumour cell lines, intrinsically resistant human tumour cells on average have higher RBE than radiosensitive cells.

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