Comparative myocardial uptake kinetics of hexakis (alkylisonitrile) technetium (I) complexes: effect of lipophilicity. *Invest Radiol* 1989;24:25–29.

Cumali Aktolun
Hammersmith Hospital
London, England

Modeling of Tumor Uptake to Determine the Time-Dose-Fractionation Effect in Radioimmunotherapy

TO THE EDITOR: The recent interesting discussion by Rao and Howell (*1*) has introduced the concept of time-dose-fractionation (TDF) into radioimmunotherapy (RIT). In TDF, the absorbed dose rate is considered to be clinically important (*2*). Using theoretical arguments, the authors proposed that TDF be used in both treatment planning and radionuclide selection for RIT. While we agree that TDF is significant in ^{226}Ra brachytherapy (*2*), we feel that Rao and Howell may not have justified its inclusion in beta-therapy or considered the most general form of the TDF computation needed for a radionuclide source.

Briefly, Rao and Howell (*1*) assumed that a tumor TDF estimate could be done using the simple formula:

$$TDF = 0.122 r_0^{1.35} \tau_e. \qquad \text{Eq. 1}$$

In the above equation, r_0 was the "initial" dose rate (cGy/hr) whose exponent (1.35) was an empirical constant previously derived from various clinical brachytherapy trials using ^{226}Ra sources (*3–5*). The time quoted, τ_e (days), was an effective time in the tumor given by:

$$\tau_e = T_{e,t} - T_{eu,t}, \qquad \text{Eq. 2}$$

with $T_{e,t}$ being the effective half-life and $T_{eu,t}$ the effective uptake half-time for the lesion. Since such times involve both biological as well as physical decay, the physical half-life of the radionuclide will have an important impact on the TDF estimate (*1*). By comparing various estimated TDF values, the authors argued for using radionuclides with extended physical half-lives in RIT.

Initially, one may question the applicability of TDF concepts developed with a pure photon-emitter such as an encapsulated source of ^{226}Ra in the RIT context of pure beta sources such as ^{90}Y or ^{32}P. A proof of dose rate effects with beta emitters seems necessary, but was not described in tumors by Rao and Howell (*1*).

Two numerical difficulties also occur with the practical use of Equations 1 and 2. Most importantly, it is not clear what rate is to be utilized. In biodistribution studies, absorbed dose rate necessarily begins at zero and goes through a maximum before becoming zero again at long intervals (*6*). The authors (*1*) elected to refer to an "extrapolated" value, apparently meaning something different from the initial or the maximum value of the r(t) curve. Also problematic was the use of a simple time difference, as in Equation 2, to account for the time integration of dose rate.

To eliminate both numerical problems, we suggest that one

TABLE 1
Time-Dose-Fractionation Factors (TDFs) for Three Radionuclides

Yttrium-90	Condition 1* $T_{e,t}$ = 2.2 d $T_{eu,t}$ = 1.1 d $\tau_{e,t}$ = 1.1 d							
r_0, Dose rate (cGy/hr)	2.5	5.0	10	20	30	40	50	100
TDF (Ref. 1)	0.462	1.21	2.97	7.7	13.2	19.58	26.4	67.32
TDF (This work)	0.320	0.817	2.08	5.31	9.18	13.53	18.29	46.63
Iodine-131	Condition 1* $T_{e,t}$ = 5.0 d $T_{eu,t}$ = 1.5 d $\tau_{e,t}$ = 3.5 d			Condition 2 $T_{e,t}$ = 10.0 d $T_{eu,t}$ = 6.5 d $\tau_{e,t}$ = 3.5 d				
r_0, Dose rate (cGy/hr)	2.5	5.0	10	20	30	40	50	100
TDF (Ref. 1)	1.5	3.8	9.6	24.4	42.2	62.2	84.0	214.0
TDF (This work, condition 1)	1.20	3.06	7.80	19.89	34.39	50.70	68.53	174.69
TDF (This work, condition 2)	0.87	2.22	5.67	14.45	24.97	36.83	49.77	126.87
Phosphorus-32	Condition 1* $T_{e,t}$ = 6.9 d $T_{eu,t}$ = 1.6 d $\tau_{e,t}$ = 5.3 d							
r_0, Dose rate (cGy/hr)	2.5	5.0	10	20	30	40	50	100
TDF (Ref. 1)	2.23	5.83	14.31	37.1	63.6	94.34	127.2	324.36
TDF (This work)	1.91	4.87	12.41	31.63	54.69	80.64	108.99	277.82

*Condition 1 is from Ref. 1 and is based on biological rate constants for an unspecified antibody.

integrate over the rate as a function of time, as initially indicated by Orton (2). Using Orton's (2) numerical constant, we set:

$$\text{TDF(tumor)} = 0.114 \int_0^\infty r(t)^{1.35}\, dt. \qquad \text{Eq. 3}$$

Next, we assumed that the tumor dose rate function could be mathematically modeled as:

$$r(t) = r_0[\exp(-\lambda_1 t) - \exp(-\lambda_2 t)], \qquad \text{Eq. 4}$$

where λ_1 represents the effective rate constant and λ_2 the effective uptake rate constant. A curve such as Equation 4 increases from zero at t = 0, goes through a maximum and returns to the origin at long times as we expect for tumor uptake of a radiotracer. The two rate constants are related to the effective half-times (T) described by Rao and Howell (1) via the usual form: $\lambda = 0.693/T$ whereby each rate constant contained a sum of biological (b) and physical (p) rate constants; e.g., $\lambda_1 = \lambda_{b1} + \lambda_p$.

We have performed several integrations of our Equation 3 using Equation 4 as the rate function. We then compared those results with Rao and Howell's approximation of Equation 1 using the biological kinetic parameters (condition 1) as supplied by those authors (1). The results are given in Table 1. We note that our results are approximately 70% of those given by Rao and Howell (1). Moreover, if we kept the difference of times (τ_e) fixed but allowed $T_{e,t}$ to increase twofold (condition 2), the result of our ^{131}I calculation became only 60% of that shown in Rao and Howell (1). This contradicted the assertion (1) that the TDF depends only on τ_e.

Accepting that tumor dose rate effects are indeed operative with pure beta sources, we are led to several conclusions regarding TDF in radioimmunotherapy. First, we believe that a more general absorbed dose rate integration should be done—using, if available, the actual tumor uptake curve(s) for estimation of TDF. Next, Tables 2, 3, and 4 shown in Rao and Howell (1) are not readily applicable in clinical practice since they depend upon variables which are either unclear (r_0) or incorrect (the time integral of the rate). Finally, although the authors suggest (1) that longer-lived radionuclides should be used in RIT, we would caution that this conclusion depends upon the stability of the bifunctional chelating agent used. We know of no agent which has a zero off rate; i.e., is permanently stable in plasma. Thus, long-lived potential RIT radionuclides such as ^{32}P may be leachable from the antibody leading to altered biodistributions involving increased bone marrow uptake.

REFERENCES

1. Rao DV, Howell RW. Time-dose-fractionation in radioimmunotherapy: implications for selecting radionuclides. *J Nucl Med* 1993;34:1801–1810.
2. Orton CG. Time-dose factors (TDFs) in brachytherapy. *Brit J Radiol* 1974; 47:603–607.
3. Patterson R. *The treatment of malignant disease by radiotherapy*, second edition. Baltimore: Williams and Wilkins; 1963:210.
4. Ellis F. *Time and dose relationships in radiation biology as applied to radiotherapy* (BNL50203 (C-57)). Upton, NY: Brookhaven National Lab; 1969:313.
5. Mitchell JS. *Studies in radiotherapeutics*. Oxford: Blackwell; 1960:234.
6. Beatty BG, Paxton RJ, Hawthorne MF, et al. Pharmacokinetics of an anti-carcinoembryonic antigen monoclonal antibody conjugated to a bifunctional transition metal carborane complex (venus flytrap cluster) in tumor-bearing mice. *J Nucl Med* 1993;34:1294–1302.

An Liu
Lawrence E. Williams
Andrzej J. Demidecki
Andrew A. Raubitschek
Jeffrey Y.C. Wong
UCLA Medical Center,
Los Angeles, California
City of Hope National Medical Center,
Duarte, California

REPLY: We appreciate the interest of Liu et al. in our recent publication (1) on the use of a time-dose-fractionation (TDF) approach to select optimal radionuclides for radioimmunotherapy. Liu et al. seem to be primarily concerned about the use of TDF for therapy with internal beta emitters, as well as our not considering the most general form of the TDF computation for internal emitters.

Liu et al. question the existence of a dose-rate effect for beta emitters, and therefore question the applicability of the TDF approach which was formulated based on clinical brachytherapy data with ^{226}Ra (2). Dose rate effects for low-LET radiations (e.g., β, γ, χ) are well known in radiobiology and have been a topic that has attracted considerable attention in RIT. As pointed out in the introduction of our paper (1), Fowler (3) has used the linear-quadratic model to suggest that dose-rate effects indeed play a role in radioimmunotherapy. This is further substantiated in the recent AAPM Nuclear Medicine Committee Task Group No. 2 Report on Dosimetry of Radiolabeled Antibodies where Langmuir et al. (4) discuss evidence of dose-rate effects for beta emitters. Clearly, only small dose-rate effects are expected for short-lived radionuclides such as ^{90}Y and such effects may be difficult to discern experimentally considering the uncertainties inherent in internal dosimetry. This is supported by our TDF calculations ((1), Table 8, row 8) which show that ^{90}Y can be about as effective as the standard 60 Gy of ^{226}Ra gamma rays delivered over 7 days. However, the same TDF calculations demonstrate that dose-rate effects can be more substantial when effective half-lives are increased through the use of longer-lived radionuclides such as ^{32}P and ^{114m}In.

Liu et al. also expressed concern regarding our use of an approximate form of the TDF expression for incorporated radionuclides. We have chosen this approach for the sake of simplicity without unduly sacrificing accuracy given the uncertainties in determining tumor activity and absorbed dose. This rationale is explained in detail below. The authors are correct in that the most general form of the dose rate function r(t) will provide the most accurate TDF values. Accordingly, Liu et al. have appropriately suggested that the following traditional function for the dose rate be used:

$$r(t) = r_0(e^{-0.693t/T_e} - e^{-0.693t/T_{eu}}), \qquad \text{Eq. 1}$$

where T_e and T_{eu} are the effective clearance half-life and effective uptake half-time in the tissue, respectively, and r_0 is the extrapolated "initial" dose-rate. Given that they have conveniently used r_0 in Equation 1, we fail to understand their lack of appreciation of the definition of the extrapolated "initial" dose-rate. In any case, the total dose D delivered to the tissue is obtained by integrating Equation 1 from 0 to ∞ which yields: