Time-Dose-Fractionation in Radioimmunotherapy: Implications for Selecting Radionuclides

Dandamudi V. Rao and Roger W. Howell

Department of Radiology, University of Medicine and Dentistry of New Jersey, Newark, New Jersey

As currently practiced, the doses delivered to tumors in radioimmunotherapy are less than desirable primarily because of dose-limiting bone marrow toxicity, thus reducing the therapeutic efficacy of this modality. The biological effectiveness of internal radionuclide therapy depends on the total dose, the rate at which it is delivered, and the fractionation schedule of the radiolabeled antibodies administered. A new approach, based on time-dose-fractionation (TDF), which has been used in conventional radiotherapy, is advanced. This approach incorporates differences in dose rates, biological half-lives of the antibodies, physical half-lives of the radionuclides employed and the total doses needed for a given biological effect. The TDF concept is illustrated with several relevant examples for radioimmunotherapy. Based on the TDF approach, it is proposed that under certain biological conditions radionuclides with physical half-lives that are 1–3 times the biological half-life of the radiolabeled antibodies in the tumor are more likely to deliver sterilization doses to tumors than the shorter-lived nuclides presently in use unless precluded by specific activity considerations. Several radionuclides that meet this criteria are suggested with ^{32}P being the most promising among them. Finally, a practical method for treatment planning in radioimmunotherapy using TDF factors is recommended.

J Nucl Med 1993; 34:1801–1810

Cancer radioimmunotherapy (RIT) is a modality of considerable interest to the medical community. The limited success of RIT so far has been attributed to a number of problems. The initial dose rates and the total doses delivered to tumors are generally low in RIT. A recent analysis of dose-rate effects in RIT by Fowler (*1*) shows that initial dose rates of 10–20 cGy/hr and total doses of 1500–2000 cGy, delivered with effective half-lives of the order of a few days, can only kill 2–3 logs of cancer cells out of the 9–10 logs required for total eradication of the tumor. In conventional radiotherapy, however, doses of about 60 Gy are necessary to eradicate the tumor. Such high doses are obviously difficult to reach in RIT with the radiolabeled antibodies currently in use without compromising the critical function of the bone marrow. This is further complicated by the fact that the radiation dose to the tumor decreases exponentially, the nature of which is determined by the physical half-life (T_p) of the radionuclide and the biological half-life (T_b) of the monoclonal antibodies (Mabs) in the tumor. To compensate for the resulting dose-rate effect, Fowler (*1*) suggested that RIT will require a 20% higher dose than conventional radiotherapy (2 Gy fractions) when the RIT dose is delivered with an effective half-life (T_e) of a few days. It is clear that the ultimate biological consequence of irradiating tissue with internal radionuclides is determined not only by the total dose, but also by the initial dose rate and the length of irradiation time (effective half-life) as well as additional biological factors (e.g., proliferation rates of normal and tumor tissues). This concept is valid for normal tissues as well as tumors.

The goal in RIT is to deliver a sufficiently large dose to the tumor in a short period of time (to minimize dose-rate effects) without unduly affecting the normal tissues such as bone marrow. This may be accomplished under certain ideal conditions: (1) rapid tumor uptake of the radiolabeled Mabs; (2) relatively long effective half-life ($T_{e,t}$) in the tumor; (3) short effective half-lives in normal organs and whole body; and (4) high tumor-to-normal tissue uptake ratio. These conditions are seldom satisfied clinically, thereby explaining the limited success of RIT thus far. Tumor uptake in humans is generally slow with typical effective uptake half-times ($T_{eu,t}$), the time required to reach half the maximum activity, in the range of 1–2 days (*2,3*). The effective half-life (T_e) of the radioactivity is usually in the range of 2–7 days in the tumor and 1–4 days in the whole body, depending on the tumor type, Mab, and the physical half-life of the radiolabel (*2–5*). The tumor uptake of Mabs is highly dependent on the size of the tumor as reported by Macey et al. (*2*). The larger the tumor mass, the lower the tumor uptake (activity/g) and hence, the lower the tumor-to-background ratio (*2*). Given these general conditions in RIT, one approach to improve the therapeutic efficacy is to increase the effective half-life of the radiolabeled Mab in the tumor without significantly altering the effective half-life in the critical organs. This of course is only feasible if the biological half-life of the Mab in the tumor is longer than in the critical organs. Since one

Received Mar. 18, 1993; revision accepted May 25, 1993.

For correspondence and reprints contact: Dandamudi V. Rao, PhD, Professor of Radiology, Division of Radiation Research, MSB F-451, UMDNJ-New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103.

TABLE 1
Explanation of Symbols

Symbol	Explanation
T_p	Physical half-life of the radionuclide
T_b	Biological half-life of the radiolabeled antibody
T_e	Effective half-life of the radiolabeled antibody
T_u	Biological uptake half-time
$T_{b,t}$	Biological half-life in the tumor
$T_{u,t}$	Biological uptake half-time in the tumor
$T_{b,B}$	Biological half-life in the body
T_{eu}	Effective uptake half-time ($T_{eu} = (T_p X T_u)/(T_p + T_u)$)
τ_e	Effective time ($\tau_e = T_e - T_{eu}$)
$T_{e,t}$	Effective half-life in the tumor
$T_{eu,t}$	Effective uptake half-time in the tumor
$\tau_{e,t}$	Effective time in the tumor
$T_{e,B}$	Effective half-life in the body
r_t	Dose rate to the tumor
r_B	Dose rate to the whole body
r_o	Initial dose rate
$r_{o,t}$	Initial dose rate to the tumor
$r_{o,B}$	Initial dose rate to the whole body
TDF	Time dose fractionation factor
TDF_t	Tumor TDF
TDF_B	Whole body TDF
λ	Decay constant of the radionuclide
λ_e	Effective decay constant of the radionuclide
T/NT	Tumor-to-nontumor (body) ratio

has only limited control over the biological half-lives, the effective half-lives of the radiolabeled Mabs can only be readily manipulated by altering the physical half-life of the radionuclide employed. The selection of the radionuclide appropriate to the biological situation therefore becomes important. To date, the only radionuclides that have been emphasized for use in RIT (*6–8*) have been those with relatively short physical half-lives of less than 10 days (e.g., (^{131}I), (^{90}Y), (^{186}Re) and (^{211}At)). If the biological half-life of Mabs in the tumors is much longer than the biological half-life in the normal tissues, radionuclides with physical half-lives longer than a few days may offer a distinct advantage in that the effective half-life of the radiolabeled Mabs in tumors would be correspondingly longer. Furthermore, when the postadministration time required for maximum tumor uptake is comparable to or longer than the physical half-life of the radionuclide, relatively more disintegrations occur in the normal tissues thereby limiting the activity that can be administered. These considerations suggest that when tumor uptake time and biological half-life are relatively long, radionuclides with longer physical half-lives can be more effective in achieving the maximum tumor dose with minimum damage to critical tissues which is necessary for success with RIT.

In this paper, the concept of time-dose-fractionation (TDF) factors (*9–11*), is introduced and adapted for RIT. These factors are valuable in arriving at biologically equivalent doses when different dose rates and regimens are involved in the treatment. The usefulness of TDF factors in RIT is discussed and illustrated with several examples. Using the TDF concept, it is quantitatively demonstrated that radionuclides with longer physical half-lives can play a role in RIT. Accordingly, several radionuclides with desirable properties are suggested and TDF factors are tabulated for the sake of convenience. Finally, an approach for treatment planning in RIT using TDF factors is described. The symbols used to describe various quantities in this paper are given in Table 1 for ready reference.

TIME-DOSE-FRACTIONATION

In conventional radiotherapy, three different techniques are available to deliver the radiation dose to tumors: (1) fractionated doses using external beams of radiation; (2) continuous exposure at constant dose rates by long-lived sealed-source implants ((^{226}Ra), (^{137}Cs)); and (3) short-lived sealed-source implants which deliver exponentially decreasing dose rates ((^{198}Au), (^{222}Rn), (^{125}I), (^{192}Ir)). These different treatment regimens differ in time, dose and fractionation patterns, and therefore may not be equally effective for a given total absorbed dose to the tumor. Recognizing the need to standardize prediction of the biological response for the different treatment regimens, Ellis (*12*) introduced the concept of nominal standard dose (NSD). This concept was later simplified by the introduction of TDF factors for fractionated therapy (*9*) and brachytherapy (*10*). The standard treatment regimen chosen for the purpose of comparison with other techniques was 60 Gy delivered over 7 days with a sealed (radium-226) ^{226}Ra source (*10*). This standard regimen was assigned a TDF factor of 100 (*10*). Accordingly, when the TDF factor for a given regimen is less than 100, such treatment will be less effective than the standard ^{226}Ra treatment and vice versa.

When ^{226}Ra therapy is given at different dose rates for different lengths of time, clinical experience shows that there is an iso-effect relationship between the dose rate and the irradiation time (*10*). Using this relationship, and requiring the TDF factor for 60 Gy in 7 days to be 100, a general equation for the TDF factor was derived (*10*):

$$TDF = 4.76 \times 10^{-3} r_o^{1.35} T_{eq}, \qquad \text{Eq. 1}$$

where r_o is the initial dose rate (in cGy per hour), and

$$T_{eq} = \frac{1 - e^{-1.35\lambda t}}{1.35\lambda}, \qquad \text{Eq. 2}$$

where λ is the physical decay constant in h^{-1}. For temporary application of long-lived radionuclides such as (^{137}Cs), $T_{eq} = T$, the irradiation time (*10*). In the case of complete radioactive decay (i.e., permanent application of short-lived isotopes), Equation 2 reduces to $T_{eq} = 1/(1.35\lambda)$ (*10*). Substitution of T_{eq} into Equation 1 yields:

$$TDF = \frac{4.76 \times 10^{-3} r_o^{1.35}}{1.35\lambda}. \qquad \text{Eq. 3}$$

For sealed sources, λ is simply $0.693/T_p$. The above equation can be easily adapted to the situation in RIT. When radionuclides are administered to the patient, $\lambda_e = 0.693/T_e$ where the effective half-life $T_e = (T_p \times T_b)/(T_p + T_b)$. Substitution for λ in Equation 3 in terms of T_e (in days) gives:

$$TDF = 0.122 r_o^{1.35} T_e. \quad \text{Eq. 4}$$

Equation 4 is only valid for instantaneous uptake of the radioactivity by the organ of interest. As previously pointed out, the tumor uptake is usually slow. In these situations, the effective uptake half-time T_{eu} may be comparable to T_e in a given tissue and therefore T_e in Equation 4 should be replaced with the *effective time* $\tau_e = (T_e - T_{eu})$, where the effective uptake half-time $T_{eu} = (T_p \times T_u)/(T_p + T_u)$ (*13*), and T_u is the biological uptake half-time. Then the "initial" dose rate r_o is the extrapolated value from the dose rate versus time curve at time t = 0 (*13*). Hence, the general TDF equation for RIT treatment planning can be written as follows:

$$TDF = 0.122 r_o^{1.35} \tau_e. \quad \text{Eq. 5}$$

It should be noted that the TDF factor is proportional to $r_o^{1.35}$ and τ_e. When the effective half-life in the tumor is short (<1 day), extrapolation of the dose rate to time zero may yield a high initial dose rate r_o, and hence a high TDF value. Caution should be exercised when using the above equation for very short effective times with comparable uptake times. Deriving the TDF equation in terms of maximum dose rate, which occurs when the uptake is at its peak, may alleviate this problem. Nevertheless the above equation is adequate to illustrate the usefulness of the TDF concept.

Several important but simple features of TDF factors need to be mentioned: (1) TDF factors are additive (TDF = $TDF_1 + TDF_2 + \ldots$), meaning multiple injections of radiolabeled Mabs as well as combination treatment regimens such as external beam therapy followed by RIT can be easily accommodated. (2) When the relative biological effectiveness (RBE) of the radiation is >1 and the effectiveness of the radiation is dose-rate dependent, RBE corrections to the initial dose rates are required before TDF factors are calculated. (3) TDF factors are not limited to RIT, they can be used to calculate biologically equivalent doses in all situations where radionuclides are administered to patients for therapy. (4) Depending on the radiation sensitivity of the tumor involved, TDF factors other than the standard value of 100 may be required. This approach accommodates treatment planning based on clinical experience for a given tumor type.

Despite its simplicity, there are several limitations to the approach presented here. It has been suggested (*14,15*) that the TDF model is only appropriate for early effects while a different formalism is required for late effects. Furthermore, this approach does not adequately address cell repopulation (i.e., differences in the rate of proliferation in tumors and normal tissues) (*14*). For example, when low dose rates are employed over an extended period of time, it has been shown that a dose rate of at least 3 cGy/hr is required just to overcome cell proliferation before any reduction in cell population can be achieved (*1*). Consequently, the TDF model presented here may not properly predict the biological response when tissues with high cell proliferation rates are irradiated with prolonged low dose rates. Additional concerns are the macroscopic and microscopic dose heterogeneity in tumors and normal organs resulting from nonuniform distribution of the radiolabeled Mabs that are well recognized in RIT. The TDF approach presented here, which employs average organ absorbed doses, does not take such dose heterogeneities into account (*16*). In an effort to overcome some of the deficiencies in the basic TDF model, most calculations in radiotherapy are now performed using the linear quadratic model (*17*). However, it should be noted that this model also has shortcomings with respect to the overall treatment time and lack of a proliferation term for the irradiated tissue. Hence, in view of the above considerations, care should be exercised in using the present TDF model in extreme cases, particularly with respect to differences in proliferation rates and radiosensitivities of tumor and normal tissues. In RIT, however, perhaps a greater impediment to predicting the biological effect is our limited ability to quantify organ/tumor activity and its distribution within the tissues and thereby accurately calculating the absorbed doses to the tumor and normal organs. Nevertheless, the above approach should serve as a useful first-order approximation for RIT treatment planning.

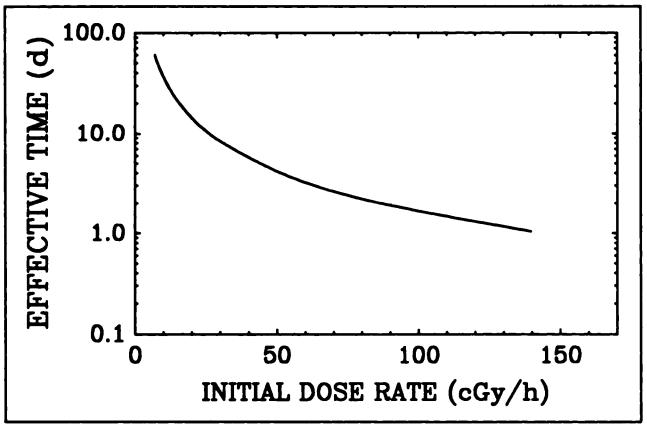

FIGURE 1. Iso-effect curve for TDF = 100. Given the τ_e in days, the initial dose rate (cGy/hr) can be obtained from the graph.

For the convenience of implementing the TDF concept in RIT, the iso-effect curve for a TDF factor of 100 is shown in Figure 1. For a given effective time τ_e, the initial dose rate required to deliver a total dose that is biologically equivalent to 60 Gy in 7 days from ^{226}Ra, can be easily read from Figure 1. When treatments are planned at TDF factors other than 100, Tables 2–4 may be used for most relevant values of TDF, τ_e and r_o. The application of TDF factors to the solution of typical problems encountered in RIT is illustrated by the following examples.

Calculation of Initial Dose Rate to the Organ/Tumor

Problem. In a ^{131}I Mab treatment, it is known that $\tau_{e,t}$ = 4 days in the tumor. What is the $r_{o,t}$ necessary to deliver a total dose that is biologically equivalent to the standard 6000 cGy in 7 days from ^{226}Ra?

TABLE 2
Time Dose Fractionation Factors Factors ($0 < \tau_e < 5$ days)

Effective time (days)	Initial dose rate (cGy/hr)															
	2.5	5	7.5	10	12.5	15	20	25	30	40	50	60	70	80	90	100
0.25	0.11	0.27	0.46	0.68	0.92	1.2	1.7	2.4	3.0	4.4	6.0	7.7	9.5	11.3	13.3	15.3
0.50	0.21	0.54	0.93	1.4	1.8	2.4	3.5	4.7	6.0	8.9	12.0	15.4	18.9	22.6	26.5	30.6
0.75	0.32	0.80	1.4	2.1	2.8	3.5	5.2	7.1	9.0	13.3	18.0	23.0	28.4	34.0	39.8	45.9
1.00	0.42	1.1	1.9	2.7	3.7	4.7	7.0	9.4	12.0	17.8	24.0	30.7	37.8	45.3	53.1	61.2
1.25	0.53	1.3	2.3	3.4	4.6	5.9	8.7	11.8	15.1	22.2	30.0	38.4	47.3	56.6	66.4	76.5
1.50	0.63	1.6	2.8	4.1	5.5	7.1	10.5	14.1	18.1	26.6	36.0	46.1	56.7	67.9	79.6	91.8
1.75	0.74	1.9	3.2	4.8	6.5	8.3	12.2	16.5	21.1	31.1	42.0	53.7	66.2	79.2	92.9	107
2.00	0.84	2.1	3.7	5.5	7.4	9.5	13.9	18.8	24.1	35.5	48.0	61.4	75.6	90.6	106	122
2.25	0.95	2.4	4.2	6.2	8.3	10.6	15.7	21.2	27.1	40.0	54.0	69.1	85.1	102	119	138
2.50	1.1	2.7	4.6	6.8	9.2	11.8	17.4	23.5	30.1	44.4	60.0	76.8	94.5	113	133	153
2.75	1.2	2.9	5.1	7.5	10.2	13.0	19.2	25.9	33.1	48.9	66.0	84.4	104	125	146	168
3.00	1.3	3.2	5.6	8.2	11.1	14.2	20.9	28.3	36.1	53.3	72.0	92.1	113	136	159	184
3.25	1.4	3.5	6.0	8.9	12.0	15.4	22.6	30.6	39.2	57.7	78.0	99.8	123	147	173	199
3.50	1.5	3.8	6.5	9.6	12.9	16.5	24.4	33.0	42.2	62.2	84.0	107	132	158	186	214
3.75	1.6	4.0	7.0	10.3	13.9	17.7	26.1	35.3	45.2	66.6	90.0	115	142	170	199	230
4.00	1.7	4.3	7.4	10.9	14.8	18.9	27.9	37.7	48.2	71.1	96.0	123	151	181	212	245
4.25	1.8	4.6	7.9	11.6	15.7	20.1	29.6	40.0	51.2	75.5	102	131	161	192	226	260
4.50	1.9	4.8	8.3	12.3	16.6	21.3	31.4	42.4	54.2	79.9	108	138	170	204	239	275
4.75	2.0	5.1	8.8	13.0	17.6	22.4	33.1	44.7	57.2	84.4	114	146	180	215	252	291
5.00	2.1	5.4	9.3	13.7	18.5	23.6	34.8	47.1	60.2	88.8	120	154	189	226	265	306

Solution. By definition, a total dose of 6000 cGy in 7 days from ^{226}Ra is equal to a TDF of 100. According to Table 2, for $\tau_{e,t}$ = 4 days, r_o of 52 cGy/hr is required to give a TDF of about 100. At 52 cGy/hr, the total dose needed to be biologically equivalent to 6000 cGy in 7 days is $1.44 \times \tau_{e,t} \times r_{o,t}$ = 7188 cGy. This 20% increase in dose over the standard regimen is required to compensate for dose rate effects. A similar conclusion was reached by Fowler (*1*) using the linear quadratic model. If the maximum concentration of ^{131}I in the tumor is known, the activity necessary to deliver the prescribed dose rate can be calculated.

Fractionated Doses in RIT

Problem. In a treatment with ^{90}Y Mabs, the tumor is irradiated at an initial dose rate of 50 cGy/hr (extrapolated, t = 0) and it is known that the $T_{e,t}$ = 2.5 days and $T_{u,t}$ = 1 day in the tumor. If another dose of ^{90}Y is planned 7 days after the first injection, what activity needs to be used to obtain a total TDF = 100?

Solution. The $T_{eu,t}$ is $(2.7 \times 1)/(2.7 + 1)$ = 0.73 day, where 2.7 days is the physical half-life of ^{90}Y. Then the $\tau_{e,t} = T_{e,t} - T_{eu,t}$ = 1.77 days. From Table 2, for a $\tau_{e,t}$ of 1.77 days and an initial dose rate of 50 cGy/hr, the TDF factor is 42. Therefore, the next injection requires a TDF of 58 to obtain a total TDF = 100. Again from Table 2, for a TDF of 58 and a $\tau_{e,t}$ of 1.77 days, the initial dose rate required is 63 cGy/hr. The activity necessary for the second injection therefore is 63/50 = 1.26 times the activity used in the first injection. This calculation assumes the same $\tau_{e,t}$ for the second injection. It should be noted, however, that the $\tau_{e,t}$ may not necessarily be the same for the second injection because of HAMA and other immune responses. Similar approaches can be used to combine different treatment regimens (e.g., split doses of external beams of radiation or sealed source implants in combination with radiolabeled Mabs).

Calculation of Maximum Tolerable Dose

Problem. Assume that the bone marrow dose is the same as the whole-body dose. In ^{90}Y Mab therapy, patients have tolerated a body dose of 200 cGy and the $T_{e,B}$ is 24 hr. What body dose will be tolerated by patients if the Mabs are labeled with ^{131}I, whose $T_{e,B}$ is determined to be 4 days?

Solution. The initial dose rate from ^{90}Y to the body is 200/(1.44 × 24) = 5.8 cGy/hr. At this dose rate, for a $T_{e,B}$ of 24 hr, the TDF factor from Table 2 is 1.3. Requiring the TDF be 1.3 and using the $T_{e,B}$ of 4 days for ^{131}I Mabs, the initial dose rate from Table 2 is about 2.1 cGy/hr, for a total body dose of 290 cGy. Therefore, 200 cGy from ^{90}Y given with a $T_{e,B}$ of 24 hr is biologically equivalent to 290 cGy from ^{131}I with a $T_{e,B}$ of 4 days. The activity of ^{131}I which would deliver a total dose of 290 cGy to the body can be calculated using MIRD procedures (*18*).

RADIONUCLIDE SELECTION

Biological and Physical Half-Lives

In brachytherapy, where sealed sources are implanted, the initial dose rate is dictated by the physical half-life of the radionuclide for a given source configuration relative to the tumor. In contrast, the dose rate and the total dose to the tumor in RIT is controlled by the physical half-life as well as the biological behavior of the Mabs. It is clear from Equation 5 and the above examples that the overall therapeutic effect in RIT is primarily governed by the initial dose rate r_o and the effective time τ_e. High $r_{o,t}$ and short $\tau_{e,t}$ are desirable to minimize the dose-rate effect in tumors, whereas relatively low values of r_o and τ_e are preferred in normal tissues. The dose rate r_t for a given radionuclide in

TABLE 3
Time Dose Fractionation Factors (5 days < τ_e < 30 days)

Effective time (days)	Initial dose rate (cGy/hr)															
	2.5	5	7.5	10	12.5	15	17.5	20	22.5	25	27.5	30	32.5	35	37.5	40
5	2.1	5.4	9.3	13.7	18.5	23.6	29.1	34.8	40.8	47.1	53.6	60.2	67.1	74.2	81.4	88.8
5.5	2.3	5.9	10.2	15.0	20.3	26.0	32.0	38.3	44.9	51.8	58.9	66.3	73.8	81.6	89.5	97.7
6	2.5	6.4	11.1	16.4	22.2	28.4	34.9	41.8	49.0	56.5	64.3	72.3	80.5	89.0	97.7	107
6.5	2.7	7.0	12.1	17.8	24.0	30.7	37.8	45.3	53.1	61.2	69.6	78.3	87.2	96.4	106	115
7	2.9	7.5	13.0	19.1	25.9	33.1	40.7	48.8	57.2	65.9	75.0	84.3	94.0	104	114	124
7.5	3.2	8.0	13.9	20.5	27.7	35.4	43.6	52.3	61.3	70.6	80.3	90.4	101	111	122	133
8	3.4	8.6	14.8	21.9	29.6	37.8	46.6	55.7	65.4	75.3	85.7	96.4	107	119	130	142
9	3.8	9.7	16.7	24.6	33.3	42.5	52.4	62.7	73.5	84.8	96.4	108	121	134	147	160
10	4.2	10.7	18.5	27.3	36.9	47.3	58.2	69.7	81.7	94.2	107	120	134	148	163	178
11	4.6	11.8	20.4	30.1	40.6	52.0	64.0	76.7	89.9	104	118	133	148	163	179	195
12	5.0	12.9	22.2	32.8	44.3	56.7	69.8	83.6	98.0	113	129	145	161	178	195	213
14	5.9	15.0	26.0	38.3	51.7	66.2	81.5	97.6	114	132	150	169	188	208	228	249
16	6.7	17.2	29.7	43.7	59.1	75.6	93.1	111	131	151	171	193	215	237	261	284
18	7.6	19.3	33.4	49.2	66.5	85.1	105	125	147	170	193	217	242	267	293	320
20	8.4	21.4	37.1	54.7	73.9	94.5	116	139	163	188	214	241	268	297	326	355
22	9.3	23.6	40.8	60.1	81.3	104	128	153	180	207	236	265	295	326	358	391
24	10.1	25.7	44.5	65.6	88.7	113	140	167	196	226	257	289	322	356	391	426
26	10.9	27.9	48.2	71.1	96.1	123	151	181	212	245	279	313	349	386	423	462
28	11.8	30.0	51.9	76.5	103	132	163	195	229	264	300	337	376	415	456	497
30	12.6	32.2	56	82	111	142	175	209	245	283	321	361	403	445	488	533

the tumor is primarily determined by the maximum concentration of activity in the tumor, the speed at which the maximum concentration is achieved ($T_{eu,t}$) and the clearance pattern ($T_{e,t}$). Clinical experience of several investigators (*2,3,19*) shows that the initial tumor dose rates and total doses are low. However, even when initial dose rates are low, the total dose can be higher if $\tau_{e,t}$ is long. In that event, to compensate for the dose-rate effect, the total dose delivered must be higher than the dose required at high dose rates. Since $\tau_e = T_e - T_{eu}$, for the effective time, τ_e, to be long, the effective half-life, T_e, should be long and the effective uptake time, T_{eu}, should be negligible compared to T_e. The effective half-life in the tumor $T_{e,t}$, however, is dictated by the physical half-life T_p of the radionuclide and the biological half-life $T_{b,t}$ of the Mabs in the tumor. The radionuclides (^{90}Y, ^{131}I, ^{186}Re, ^{211}At) currently used in RIT have physical half-lives that are frequently shorter than the biological half-life in the tumor, resulting in even smaller effective half-lives, the consequence of which is rapidly decreasing dose rates. However, if longer-lived radionuclides are employed, the effective half-lives will be dominated by the biological half-lives, thus taking full advantage of $T_{b,t}$ and hence a less rapid decline in the tumor dose rate. These considerations suggest that radionuclides with longer physical half-lives may offer some advantages over the nuclides presently in use, however, specific activity considerations may be a concern (see Treatment Planning Approach). This advantage becomes even more significant when the biological half-life of the Mab in the tumor is substantially longer than the uptake time and the biological half-life in the dose-limiting normal tissues.

To further illuminate the choice of radionuclide physical half-life, consider a hypothetical radionuclide whose half-life can be varied at will while all other conditions remain constant (e.g., activity administered, biological half-lives and so forth). In addition, assume that the antibody to which the radionuclide is labeled has a 2-day biological tumor peak uptake-time and an 8-day biological half-life in the tumor. If the physical half-life of the radionuclide is set at 1 day, considerable activity will decay elsewhere in the body before the tumor activity reaches its maximum value because of the relatively long uptake time. Once the tumor activity reaches its maximum, clearance takes place with an effective half-life of 0.9 days, thereby decreasing the dose rate rapidly. This situation involving short-lived radionuclides requires high tumor-to-nontumor (T/NT) concentration ratios to facilitate treatment. In contrast, if the half-life of the radionuclide is set to 5 days, comparatively more activity reaches the tumor which subsequently decays with an effective half-life of 3 days as opposed to 0.9 days in the above case. This facilitates delivery of a relatively higher tumor dose for the same activity administered. However, to achieve this, five times higher specific activity for the radiolabeled antibodies is necessary which is in part compensated for by the lower T/NT ratio required. If the half-life of the radionuclide is set to 20 days, the tumor will be irradiated with an effective half-life of 5.7 days. In this case, a 90% gain in the effective half-life is realized but four times higher specific activity is required. Actually, the increase in specific activity needed will be somewhat less due to the increased dose to the tumor and the lower T/NT ratio now sufficient to deliver the prescribed dose to the tumor. All of these considerations are not necessary if the T/NT ratios needed for a successful outcome can be reached with radionuclides having short physical half-lives since they obviously should be used

TABLE 4
Time Dose Fractionation Factors (30 days < τ_e < 80 days)

Effective time (days)	Initial dose rate (cGy/hr)															
	1	2	3	4	5	6	7	8	9	10	12	14	16	18	20	25
30	3.7	9.3	16.1	23.8	32.2	41.2	50.7	60.7	71.1	82.0	105	129	155	181	209	283
32	3.9	10.0	17.2	25.4	34.3	43.9	54.0	64.7	75.9	87.5	112	138	165	193	223	301
34	4.2	10.6	18.3	27.0	36.5	46.6	57.4	68.8	80.6	92.9	119	146	175	206	237	320
36	4.4	11.2	19.4	28.6	38.6	49.4	60.8	72.8	85.4	98.4	126	155	186	218	251	339
38	4.6	11.8	20.4	30.2	40.8	52.1	64.2	76.9	90.1	104	133	164	196	230	265	358
40	4.9	12.5	21.5	31.7	42.9	54.9	67.6	80.9	94.9	109	140	172	206	242	279	377
42	5.1	13.1	22.6	33.3	45.0	57.6	70.9	85.0	99.6	115	147	181	217	254	293	396
44	5.4	13.7	23.7	34.9	47.2	60.4	74.3	89.0	104	120	154	189	227	266	307	414
46	5.6	14.3	24.8	36.5	49.3	63.1	77.7	93.0	109	126	161	198	237	278	321	433
48	5.9	14.9	25.8	38.1	51.5	65.8	81.1	97.1	114	131	168	207	247	290	334	452
50	6.1	15.6	26.9	39.7	53.6	68.6	84.5	101	119	137	175	215	258	302	348	471
52	6.3	16.2	28.0	41.3	55.8	71.3	87.8	105	123	142	182	224	268	314	362	490
54	6.6	16.8	29.1	42.8	57.9	74.1	91.2	109	128	148	189	233	278	326	376	509
56	6.8	17.4	30.1	44.4	60.1	76.8	94.6	113	133	153	196	241	289	339	390	527
58	7.1	18.1	31.2	46.0	62.2	79.6	98.0	117	138	159	203	250	299	351	404	546
60	7.3	18.7	32.3	47.6	64.3	82.3	101	121	142	164	210	258	309	363	418	565
65	7.9	20.2	35.0	51.6	69.7	89.2	110	131	154	178	227	280	335	393	453	612
70	8.5	21.8	37.7	55.5	75.1	96.0	118	142	166	191	245	301	361	423	488	659
75	9.2	23.3	40.4	59.5	80.4	103	127	152	178	205	262	323	387	453	523	706
80	9.8	24.9	43.0	63.5	85.8	110	135	162	190	219	280	344	412	484	557	753

under these circumstances. Yet, in many situations the current techniques provide T/NT ratios that are less than optimal. Hence, the above considerations suggest the need to select a physical half-life consistent with the biological uptake and clearance half-lives, and the specific activity requirements for a given situation.

Low Dose Rates Versus High Dose Rates

Low dose-rate treatments with longer-lived radionuclides require much higher total doses for a given biological effect in both tumors and normal tissues. Kim and Hilaris (*20*) have shown that 160 Gy from permanent implants of ^{125}I (T_p = 60 days) seeds to treat unresectable carcinoma of the lung was tolerated as well as 80 Gy from ^{222}Rn (T_p = 3.8 days) seeds with complication rates of 13% and 11%, respectively. The initial dose rates for these two modes of treatment can be easily calculated to be 7.7 cGy/hr and 61 cGy/hr for ^{125}I and ^{222}Rn, respectively. Utilizing Equation 3, the TDF values for these radionuclides at these initial dose rates are 115 for ^{125}I and 120 for ^{222}Rn, suggesting that the regimens are biologically equivalent. These data support the potential usefulness of the TDF approach for RIT in that prolonged low dose rates can be as effective as short, high dose rates. One should keep in mind, however, that when low dose rates are involved, the total dose delivered must be sufficiently high to compensate for both proliferation and dose-rate effects.

Optimal Radionuclides for RIT

A careful search was conducted for potentially useful longer-lived radionuclides for RIT, with the restriction that they emit energetic beta-particles with nearly 100% abundance. These radionuclides were further screened and those having complex gamma-ray spectra eliminated. The resulting nuclides are arranged in three groups. Table 5 lists radionuclides and their primary radiation characteristics whose physical half-lives are from 2 to 10 days. This list contains some of the radionuclides already in use. Radionuclides with intermediate half-lives in the range of 10–20 days are listed in Table 6, and those with half-lives between 20 and 60 days are grouped in Table 7. Some of the nuclides emit a few gamma-rays and these are considered to be useful for external detection. Auger electron and soft beta-emitters are not listed, although it should be noted that they may be useful in treating micrometastases and small tumors (*6,21–23*). Alpha-emitters with short half-lives (<1

TABLE 5
Beta-Emitting Radionuclides for RIT (2 days < T_p < 10 days)

Radionuclide	T_p (d)	$\bar{E}_\beta$ (MeV)	Yield* (%)	E_γ (MeV)	Yield* (%)	Reference
^{90}Y	2.67	0.935	100	—	—	*36*
^{131}I	8.04	0.192	89.4	0.365	81.2	*36*
^{186}Re	3.78	0.362	73.0	0.137	8.6	*36*
^{198}Au	2.70	0.314	98.7	0.412	95.5	*36*

*Only primary radiations are listed.

TABLE 6
Beta-Emitting Radionuclides for RIT (10 days < T_p < 20 days)

Radionuclide	T_p (d)	$\bar{E}_\beta$ (MeV)	Yield* (%)	E_γ (MeV)	Yield* (%)	Reference
^{32}P	14.26	0.695	100	—	—	*36*
^{86}Rb	18.66	0.709	91.2	1.077	8.8	*36*
^{143}Pr	13.58	0.315	100	—	—	*37*

*Only primary radiations are listed.

day), such as ^{211}At and bismuth-212 (^{212}Bi), will be of limited value given that the tumor uptake times, $T_{u,t}$, are usually longer than the physical half-life of the radionuclide, although they may play a role in RIT when they are made available for the cancer cells directly (e.g., ascites) (*6*). Considering that dose-rate effects are minimal for high-LET particles, the relatively long-lived alpha-emitter ^{210}Po (T_p = 138 days) offers an interesting possibility in RIT. Similarly, Auger electron emitters (*24–26*) such as ^{125}I may also serve as high-LET type sources and therefore may play a role in cancer therapy if ways to direct them into the cell nucleus are developed.

TREATMENT PLANNING APPROACH

Five radionuclides, ^{90}Y (2.7 days), ^{131}I (8 days), phosphorus-32 (^{32}P) (14.26 days), rubidium-86 (^{86}Rb) (18.7 days) and indium-114m (^{114m}In) (49.5 days), are selected from Tables 5–7 to provide a quantitative analysis of the effect of different physical half-lives on the T/NT ratio (tumor dose rate relative to the body dose rate at peak tumor uptake) needed to achieve a tumor TDF_t of 100 while limiting the TDF to the body. Although bone marrow is usually considered the dose-limiting organ, the body dose can be calculated more reliably than the bone marrow dose. Hence, for the purpose of this analysis, it is assumed that the body dose is the same as the bone marrow dose. Available biological data in humans with ^{131}I-labeled antibodies suggest that the average effective uptake half-time ($T_{eu,t}$) in the tumor is about 1.5 days and the effective half-lives in the tumor ($T_{e,t}$) and body ($T_{e,B}$) are 5 days and 2.5 days, respectively. Accordingly, these values are utilized to calculate the $T_{b,B}$ (3.7 days) and $T_{b,t}$ (13.4 days), and the $T_{u,t}$ (1.9 days) for the antibodies using the physical half-life of ^{131}I. It is assumed that these biological half-lives hold true regardless of the radiolabel. The values of $T_{e,B}$, $T_{e,t}$ and $T_{eu,t}$ are calculated for all of the radionuclides and the results given in Table 8. Also shown in Table 8, Row 4, are $\tau_{e,t}$ values obtained after subtracting $T_{eu,t}$ from $T_{e,t}$. It should be noted in Table 8 that while the body $T_{e,B}$'s change slowly as the physical half-lives increase, the increase in $\tau_{e,t}$ is more dramatic reaching a value of 8.6 days in the case of ^{114m}In.

Let us assume a body dose of about 300 cGy can be tolerated without serious complications. To deliver this dose, the ^{90}Y initial dose rate to the body is calculated to be $r_{o,B}$ = 5.9 cGy/hr. Using this initial dose rate and the $T_{e,B}$ = 1.5 days, a value of about 2 for TDF_B is obtained from Table 2. Requiring TDF_B = 2 for all of the radionuclides (^{90}Y, ^{131}I, ^{32}P, ^{86}Rb and ^{114m}In), the initial body dose rates for each are calculated and given in Table 8, Row 5. Tumor doses are planned at a TDF_t of 100 and the extrapolated initial dose rates to the tumor are calculated for all radionuclides (Row 8). It is interesting to note that the initial tumor dose rate varies rather dramatically from 134 cGy/hr for ^{90}Y to 29 cGy/hr in the case of ^{114m}In, whereas body dose rates drop by a factor of <2. The total doses to the body and tumor are given in Table 8, Rows 6 and 9, respectively. These are biologically equivalent doses, TDF_t of 100 for all radionuclides in the tumor, and TDF_B of 2 for all nuclides in the body. The T/NT ratios (body) are calculated for all radionuclides (Table 8, Row 11) at a time t = $2T_{eu,t}$, the postadministration time required to achieve maximum tumor uptake. Note that ratios have also been provided for TDF_B values of 0.5 and 1.0 which are equivalent to body doses of about 100 and 200 cGy, respectively, from ^{90}Y. These ratios, which are necessary to deliver the indicated total doses to the tumor and the body, depend highly on the restrictions placed on the limiting dose to the critical organ (assumed to be body for the sake of simplicity). For example, if the critical organ cannot tolerate a TDF_B of 2 (~300 cGy for ^{90}Y), then the T/NT ratio required will be higher (row 11). If the ratio is clinically

TABLE 7
Beta-Emitting Radionuclides for RIT (20 days < T_p < 60 days)

Radionuclide	T_p (d)	$\bar{E}_\beta$ (MeV)	Yield* (%)	E_γ (MeV)	Yield* (%)	Reference
^{89}Sr	50.5	0.583	100	—	—	*36*
^{91}Y	58.5	0.603	99.7	1.205	0.3	*37*
^{114m}In	49.5	0.777	94.5	0.558	3.5	*36*
^{115m}Cd	44.6	0.602	97.0	0.934	2	*37*

*Only primary radiations are listed.

TABLE 8
Dosimetry Characteristics of Radionuclides with Different Physical Half-Lives

		^{90}Y	^{131}I	^{32}P	^{86}Rb	^{114m}In
1	$T_{e,B}$-effective half-life in body (days)	1.5	2.5	2.9	3.0	3.4
2	$T_{e,t}$-effective half-life in tumor (days)	2.2	5.0	6.9	7.7	10.4
3	$T_{eu,t}$-effective tumor uptake time (days)	1.1	1.5	1.6	1.6	1.8
4	$\tau_{e,t} = (T_{e,t} - T_{eu,t})$ for tumor	1.1	3.5	5.3	6.1	8.6
5	$r_{o,B}$-initial body dose rate (cGy/h), $TDF_B = 2.0$	5.9	4.0	3.6	3.5	3.2
6	D_B-total body dose (cGy), $TDF_B = 2.0$	306	346	361	363	376
7	r_B-body dose rate (cGy/hr) at $t = 2T_{eu,t}$, $TDF_B = 2.0$	2.1	1.7	1.7	1.6	1.5
8	$r_{o,t}$-initial tumor dose rate (cGy/hr)	134	57	42	38	29
9	D_t-total tumor dose (cGy) at $TDF_t = 100$	5,100	6,900	7700	8,000	8,600
10	r_t-tumor dose rate (cGy/hr) at $t = 2T_{eu,t}$	67	38	28	28	23
11	r_t/r_B-ratio of dose rates (T/NT) required at peak tumor uptake ($t = 2T_{eu,t}$) to achieve $TDF_t = 100$					
	$TDF_B = 2.0$	32	22	17	17	15
	$TDF_B = 1.0$	53	36	28	27	25
	$TDF_B = 0.5$	88	61	47	45	42
12	Activity required (GBq), $TDF_B = 2$	7.8	25	6.3	6.5	5.1
13	Extrapolated (t = 0) activity/g of tumor (MBq) at $TDF_t = 100$	2.5	5.2	1.0	1.0	0.67
14	Specific activity required relative to ^{90}Y	1	6.2	2.1	2.8	5.0
15	Activity per cell (MBq)*, $TDF_B = 2$, $TDF_t = 100$	2.5	5.2	1.0	1.0	0.67
16	Number of radiolabeled antibodies per cells†	840	5200	1800	2300	4100
17	Maximum theoretical specific activity (TBq/mmole)	1800	600	340	260	98

*Assuming 10^9 cells per gram of tumor (2).
†Assuming one radioatom per antibody molecule.

beyond reach, the therapeutic outcome will obviously be less than desirable. The advantage of a longer physical half-life is now apparent. The T/NT ratio, for a TDF_B of 2 and TDF_t of 100, decreases from 32 (^{90}Y) to 15 (^{114m}In). Therefore, as the physical half-life of the radionuclide increases, the required ratio decreases and becomes more likely to be attained clinically. Conversely, when the biological half-life in the tumor ($T_{b,t}$) and in the body ($T_{b,B}$) decrease, the necessary T/NT ratios increase for all radionuclides (Table 8, row 11). These points regarding the effect of T_p and $T_{b,t}$ on the T/NT ratio may be clearly seen in Figure 2 where the ratio is plotted as a function of the biological half-life in the tumor.

The administered radioactivity necessary to deliver prescribed body doses is calculated for each case (Table 8, row 12) using the respective radiation spectra and assuming a 70 kg body mass. For the sake of simplicity, contributions from gamma-rays are neglected as they are usually relatively small compared to the beta-doses. Shown in Row 13 of Table 8 are the extrapolated (t = 0) activities per gram of tumor needed for a TDF_t of 100. Relative specific activities in Row 14 indicate that to achieve this TDF, an ^{114m}In-labeled Mab must have a specific activity five times higher than that of an ^{90}Y-labeled Mab. Substantially lower increases (2.1- and 2.8-fold) are needed for ^{32}P- and ^{86}Rb-labeled Mabs even though their physical half-lives are much longer than that of ^{90}Y. Interestingly, an ^{131}I-labeled Mab requires a specific activity 6.2 times that of ^{90}Y-Mab. This is primarily due to the relatively low energy nature of the beta-particles emitted in ^{131}I decay. Assuming that there are 10^9 cells per gram of tumor (2) and the activity is uniformly distributed among the cells, the activity per cell is calculated for all radionuclides (Row 15). These values suggest that the necessary cellular activity decreases by a factor of about 2.5 and 4 for ^{86}Rb and ^{114m}In, respectively, relative to ^{90}Y. Row 16 shows the number of radioatoms per cell calculated assuming one label per antibody. These values reflect the relative specific activities shown in Row 14. Finally, Row 17 gives the maximum calculated specific activities for all radionuclides.

Naturally, one may question whether the desired activities per cell can be achieved for the radionuclides listed in Table 8 given the specific activity restrictions (Row 17). Macey et al. (2) have experimentally determined that when 20 mg of ZME-018 antibody is administered, 3.5×10^4 Mabs per cell were found in human melanoma tumors, which is well below the theoretical limit of 3.6×10^6 Mab binding sites suggested by McGaughey for a 10-μm diameter cell (27). The number of radiolabeled antibodies required per cell for the five radionuclides used in our model calculations (840, 5200, 1800, 2300, 4100) are three orders of magnitude below the theoretical limit and one order of magnitude below the level achieved for a 20-mg administration of ZME-018 Mabs (2). Hence, the desired labeling can easily be achieved if carrier-free material can be produced; however, such material may not be readily available. For instance, ^{86}Rb is currently available commercially with a specific activity of 9.5 GBq/mmole, which implies that about 1 in 27,000 atoms are radioactive. This suggests that $27,000 \times 2300 = 6.2 \times 10^7$ Mabs must be on the cell surface, which is well above even the theoretical

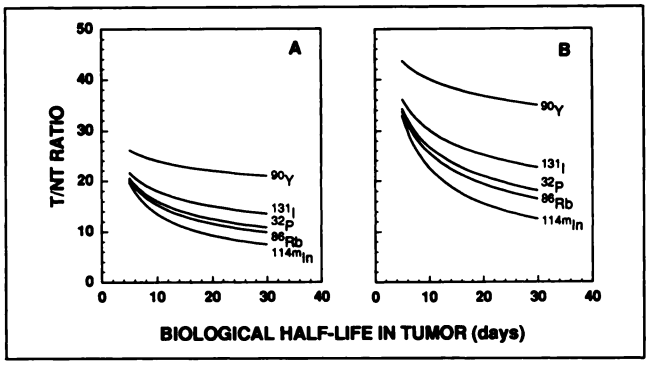

FIGURE 2. Ratio of tumor dose rate-to-nontumor (body) dose rate at maximum tumor uptake ($t = 2T_{eu,t}$) as a function of biological half-life of the radiolabeled Mab in the tumor assuming $T_{b,B} = 4$ days and $T_{u,t} = 1$ day. (A) $TDF_B = 2$, $TDF_t = 100$; (B) $TDF_B = 1$, $TDF_t = 100$. There are several noteworthy observations to be made: (1) The T/NT ratio required to deliver a $TDF_t = 100$ with longer lived radionuclides (^{32}P, ^{86}Rb, ^{114m}In) substantially decreases as the tumor biological half-life increases, whereas a less pronounced dependence is observed for short-lived radionuclides (^{90}Y). (2) For a given biological half-time in the tumor, short-lived radionuclides require higher T/NT ratios than longer lived radionuclides. (3) Comparison of A and B indicates that the T/NT ratios required to achieve $TDF_t = 100$ increase substantially as the dose-limiting TDF_B is decreased. These observations, which are relatively independent of $T_{b,B}$ and $T_{u,t}$, suggest that longer lived radionuclides may be more advantageous than their short-lived counterparts provided specific activity and minimum dose rate requirements can be met. Considering these requirements, ^{32}P is perhaps the most promising.

number of binding sites. One should keep in mind, however, that the commercially available specific activity for ^{86}Rb is several orders of magnitude lower than the theoretical specific activity of 260 TBq/mmole. The longer lived radionuclide ^{114m}In is commercially available at specific activities up to about 1 TBq/mmole. In this case, about 1 in 100 atoms are radioactive so that $100 \times 4100 = 4.1 \times 10^5$ Mabs must be labeled to the cell. This compares favorably with the 3.5×10^4 obtained by Macey et al. (*2*). Phosphorus-32 is inexpensive and readily available in carrier-free form (340 TBq/mmole). The 1800 radioactive atoms per cell (Table 8, Row 16) required in this case can be easily reached. In any case, it should be pointed out that the higher specific activities required in the case of the longer lived radionuclides are partly compensated for by the lower (factor of 2) T/NT ratios required to achieve $TDF_t = 100$ (Fig. 2 and Table 8, Row 11).

Although longer physical half-lives appear to be advantageous under certain conditions, there comes a point when selecting a longer physical half-life provides little gain in the T/NT ratio relative to the increase in the required specific activity of the labeled Mab. For example, to achieve $TDF_t = 100$ with a corresponding $TDF_B = 2$, the T/NT ratio required is essentially the same for ^{32}P and ^{114m}In (17 versus 15, Table 8) while the latter requires a Mab specific activity about 2.5 times greater. Because reduction in the required T/NT ratio to achieve $TDF_t = 100$ is minimal by going to the longer-lived ^{114m}In, the intermediate half-life ^{32}P is preferred. These comparisons are based on a biological half-life in the tumor of 13.4 days, thereby suggesting that the physical half-life of the radionuclide should be about 1–3 $T_{b,t}$. This is supported by the data in Figure 2. Admittedly, the above calculations are based on the TDF approach, which has limitations. Nevertheless, these calculations argue in favor of the use of longer-lived radionuclides, ^{32}P being the most likely candidate among them given that it may be readily obtained carrier-free.

It has been demonstrated that when specific activity considerations permit, radionuclides with longer physical half-lives are likely to offer a therapeutic advantage over short-lived nuclides, particularly when tumor uptake and activity clearance is slow compared to body clearance. The advantage diminishes as the difference in clearance patterns becomes less significant (Fig. 2). Because bone marrow toxicity is the usual dose-limiting factor in RIT, our calculations, which assume that the body is the dose-limiting organ (e.g., body dose = bone marrow dose), may not be valid (*28–30*). Nevertheless, the approach presented above is general and can be applied directly to the bone marrow if appropriate biological data and reliable methods to calculate the absorbed dose are available.

SUMMARY

The two factors that control the total dose delivered to the normal and cancerous tissues in RIT are the initial dose rate r_o and the effective time τ_e. It can be seen from Equation 5 that the TDF is proportional to $r_o^{1.35}$ and directly to τ_e. This suggests that high initial tumor dose rates $r_{o,t}$ should be preferred over long $\tau_{e,t}$. High initial dose rates to the tumor $r_{o,t}$ require near instantaneous uptake and high tumor-to-body activity concentration ratios, both of which are dictated by the antibody biokinetics. Clinical experience thus far with several antibodies shows that the initial tumor dose rates are low due to slow tumor uptakes and limited targeting (*2,3*). Increasing the $\tau_{e,t}$ is the only alternative to deliver high doses to the tumor. Therefore, depending on the tumor biological half-life, those relatively long-lived radionuclides suggested in Tables 6–7 merit serious consideration for RIT with ^{32}P being the most promising among them (*31*).

Bone marrow toxicity is considered to be the major dose-limiting factor in RIT. A further approach to overcome this problem may be to use radioprotectors such as cysteamine, DMSO, AET, etc., to increase the tolerance dose to the bone marrow. It has been shown recently that the radioprotection of spermatogonial cells with small and nontoxic amounts of cysteamine and vitamin C is significant when these chemicals are administered a few hours before the radionuclides (*32,33*). It would be of considerable interest to see if these and other similar chemicals can protect bone marrow without protecting the tumors when radionuclides are injected for RIT. If significant differential protection in favor of bone marrow can be obtained, radioprotectors may play a role in RIT. It should be noted, however, that similar attempts in conventional radiotherapy with various radioprotectors have met with limited success (*34*).

The TDF approach presented in this work incorporates differences in dose rates, biological half-lives of the antibodies, physical half-lives of the radionuclides, and total doses needed for a given biological effect in tumor and normal tissues, to intercompare the efficacy of different radiolabeled Mabs for radioimmunotherapy. With the limitations of the TDF in mind, this method can be employed even in those situations where multiple radiotherapy modalities are used. To facilitate the use of this approach in RIT, the TDF factors are conveniently tabulated (Tables 2–4). It is demonstrated that the TDF approach may be valuable for treatment planning in RIT.

Macroscopic nonuniformities, depending on the tumor size, will continue to be a problem (*21,22,35*), although energetic beta-particle emitters such as those suggested in Tables 5–7 tend to smooth the nonuniform dose distributions to some extent (*6,21,22*). Microscopic nonuniformities are mainly relevant to Auger and alpha-emitters (*6,21,22*). The stability of the radiolabel for long periods, necessary when radionuclides with long physical half-lives are employed, will also be of some concern. At low dose rates, cell proliferation may not allow reasonable prediction of biological outcome. Even when biological conditions are favorable, radiochemistry techniques and availability of high specific-activity radionuclides with longer physical half-lives may be hurdles to cross. Inasmuch as the success of radiolabeled Mab therapy hinges on understanding and resolving several problems, the work presented in this paper is an attempt to address some of them.

ACKNOWLEDGMENTS

The authors thank Michael Azure, Ellen Angyal, Venkat Narra and Murty Goddu for their assistance in preparing the manuscript, and Kandula S.R. Sastry for his helpful comments. This work was supported by USPHS grant # CA-32877 and UMDNJ Foundation grant # 26-93.

REFERENCES

1. Fowler JF. Radiobiological aspects of low dose rates in radioimmunotherapy. *Int J Radiat Oncology Biol Phys* 1990;18:1261–1269.
2. Macey DJ, Denardo SJ, Denardo GL, Goodnight JK, Unger MW. Uptake of indium-111-labeled monoclonal antibody ZME-018 as a function of tumor size in a patient with melanoma. *Am J Physiol Imag* 1988;3:1–6.
3. Order SE, Klein JL, Ettinger D, Alderson P, Siegelman S, Leichner P. Phase I-II study of radiolabeled antibody integrated in the treatment of primary hepatic malignancies. *Int J Radiat Oncol Biol Phys* 1980;6:703–710.
4. Breitz HB, Weiden PL, Vanderheyden J-L, et al. Clinical experience with rhenium-186-labeled monoclonal antibodies for radioimmunotherapy: results of Phase I trials. *J Nucl Med* 1992;33:1099–1112.
5. Goldenberg DM, Horowitz J, Sharkey RM, et al. Targeting, dosimetry, and radioimmunotherapy of B-cell lymphomas with iodine-131-labeled LL2 monoclonal antibody. *J Clin Oncol* 1991;9:548–564.
6. Humm JL. Dosimetric aspects of radiolabeled antibodies for tumor therapy. *J Nucl Med* 1986;27:1490–1497.
7. Jungerman JA, Yu KP, Zanelli CI. Radiation absorbed dose estimates at the cellular level for some electron-emitting radionuclides for radioimmunotherapy. *Int J Appl Isot* 1984;35:883–888.
8. Wessels BW, Rogus RD. Radionuclide selection and model absorbed dose calculations for radiolabeled tumor associated antibodies. *Med Phys* 1984; 11:638–645.
9. Orton CG, Ellis F. A simplification in the use of the NSD concept in practical radiotherapy. *Br J Radiol* 1973;46:529–537.
10. Orton CG. Time-dose factors (TDFs) in brachytherapy. *Br J Radiol* 1974; 47:603–607.
11. Orton CG, Webber BM. Time-dose factor (TDF) analysis of dose rate effects in permanent implant dosimetry. *Int J Radiat Oncol Biol Phys* 1977;2:55–60.
12. Ellis F. Fractionation in radiotherapy. In: Deeley TJ, Wood CAP, eds. *Modern trends in radiotherapy*. London: Butterworth; 1967:34–51.
13. Goodwin PN, Rao DV. *An introduction to the physics of nuclear medicine*. Springfield, IL: Thomas; 1977:127–136.
14. Fowler JF. What next in fractionated radiotherapy? *Br J Cancer* 1984;49: 285–300.
15. Orton CG, Cohen L. A unified approach to dose-effect relationships in radiotherapy. I: Modified TDF and linear quadratic equations. *Int J Radiat Oncol Biol Phys* 1988;14:549–556.
16. Orton CG. A unified approach to dose-effect relationships in radiotherapy. II: Inhomogeneous dose distributions. *Int J Radiat Oncol Biol Phys* 1988; 14:557–560.
17. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol* 1985;58:515–528.
18. Loevinger R, Budinger TF, Watson EE. *MIRD primer for absorbed dose calculations, revised*. New York: The Society of Nuclear Medicine; 1991.
19. Order SE, Klein JL, Ettinger D, Alderson P, Siegelman S, Leichner P. Use of isotopic immunoglobulin in therapy. *Cancer Res* 1980;40:3001–3007.
20. Kim JH, Hilaris BS. Iodine-125 source in interstitial tumor therapy. *Am J Roentgenol* 1975;123:163–169.
21. Howell RW, Rao DV, Sastry KSR. Macroscopic dosimetry for radioimmunotherapy: nonuniform activity distributions in solid tumors. *Med Phys* 1989;16:66–74.
22. Howell RW, Rao DV, Haydock C. Dosimetry techniques for therapeutic applications of incorporated radionuclides. In: Adelstein SJ, Kassis AI, Burt RW, eds. *Dosimetry of administered radionuclides*. Washington, D.C.: American College of Nuclear Physicians; 1990:215–256.
23. Sastry KSR, Haydock C, Basha AM, Rao DV. Electron dosimetry for radioimmunotherapy: optimal electron energy. *Radiat Prot Dosim* 1985;13: 249–252.
24. Sastry KSR, Rao DV. Dosimetry of low energy electrons. In: Rao DV, Chandra R, Graham M, eds. *Physics of nuclear medicine: recent advances*. New York: American Institute of Physics; 1984:169–208.
25. Howell RW. Radiation spectra for Auger-electron emitting radionuclides: report No. 2 of AAPM Nuclear Medicine Task Group No. 6. *Med Phys* 1992;19:1371–1383.
26. Rao DV, Narra VR, Howell RW, Govelitz GF, Sastry KSR. In vivo radiotoxicity of DNA-incorporated I-125 compared with that of densely ionising alpha-particles. *Lancet* 1989;II:650–653.
27. McGaughey C. Feasibility of tumor immunoradiotherapy using radioiodinated antibodies to tumor-specific cell membrane antigens with emphasis on leukemias and early metastases. *Oncology* 1974;29:302–319.
28. Langmuir VK. Radioimmunotherapy: clinical results and dosimetric considerations. *Nucl Med Biol* 1992;19:213–225.
29. Yorke ED, Beaumier PL, Wessels BW, Fritzberg AR, Morgan JAC. Optimal antibody-radionuclide combinations for clinical radioimmunotherapy: a predictive model based on mouse pharmacokinetics. *Nucl Med Biol* 1991; 18:827–835.
30. Siegel JA, Pawlyk DA, Lee RE, et al. Tumor, red marrow and organ dosimetry for ^{131}I-labeled anti-carcinoembryonic antigen monoclonal antibody. *Cancer Res* 1990;50(suppl):1039–1042.
31. Britton KE, Mather SJ, Granowska M. Radiolabelled monoclonal antibodies in oncology. III. Radioimmunotherapy. *Nucl Med Commun* 1991;12: 333–347.
32. Rao DV, Narra VR, Howell RW, Sastry KSR. Biological consequence of nuclear versus cytoplasmic decays of I-125: cysteamine as a radioprotector against Auger cascades in vivo. *Radiat Res* 1990;124:188–193.
33. Narra VR, Howell RW, Sastry KSR, Rao DV. Vitamin C as a radioprotector against ^{131}I in vivo. *J Nucl Med* 1993;34:637–640.
34. Livesey JE, Reed DJ. Chemical protection against ionizing radiation. In: Lett JT, Ehmann UK, Cox AB, eds. *Advances in radiation biology*. New York: Academic Press; 1987:285–340.
35. Wessels BW, Griffith MH. Miniature thermoluminescent dosimeter absorbed dose measurements in tumor phantom models. *J Nucl Med* 1986; 27:1308–1314.
36. Weber DA, Eckerman KF, Dillman LT, Ryman JC. *MIRD: radionuclide data and decay schemes*. New York: Society of Nuclear Medicine; 1989.
37. Browne E, Firestone RB. *Table of radioactive isotopes*. New York: Wiley; 1986.