Advanced Drug Delivery Reviews 60 (2008) 1402–1406

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Alpha-particles for targeted therapy ☆

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ARTICLE INFO

Article history:
Received 18 October 2007
Accepted 16 April 2008
Available online 23 April 2008

Keywords:
Alpha-particle
Targeted therapy
Dosimetry

ABSTRACT

Alpha-particles are helium nuclei that deposit DNA damaging energy along their track that is 100 to 1000 times greater than that of conventionally used beta-particle emitting radionuclides for targeted therapy; the damage caused by alpha-particles is predominately double-stranded DNA breaks severe enough so as to be almost completely irreparable. This means that a small number of tracks through a cell nucleus can sterilize a cell and that, because the damage is largely irreparable, alpha-particle radiation is not susceptible to resistance as seen with external radiotherapy (e.g., in hypoxic tissue). The ability of a single track to influence biological outcome and the stochastic nature of alpha-particle decay require statistical or microdosimetric techniques to properly reflect likely biological outcome when the biologically relevant target is small or when a low number of radionuclide decays have occurred. In therapeutic implementations, microdosimetry is typically not required and the average absorbed dose over a target volume is typically calculated. Animal and cell culture studies have shown that, per unit absorbed dose, the acute biological effects of alpha-particles are 3 to 7 times greater than the damage caused by external beam or beta-particle radiation. Over the past ten to 15 years, alpha-particle emitting radionuclides have been investigated as a possible new class of radionuclides for targeted therapy. Results from the small number of clinical trials reported to date have shown efficacy without significant toxicity.

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Contents

1. Introduction

Alpha-particles are charged particles made up of two protons and two neutrons. Alpha-particle emitting radionuclides are of interest in targeted therapy because of the short range and high linear energy transfer (LET) of these emissions. The former provides the specificity to target a chosen cell population with minimal effect on non-targeted cells; the latter leads to a high frequency of double-stranded DNA damage, much of which is irreparable. The practical implications of this and the distinction between alpha-particles and the more widely used beta-particle emitters (e.g., ^{131}I and ^{90}Y) for targeted radionuclide therapy are that it is possible to sterilize individual tumor cells solely from self-irradiation with alpha-particle emitters while this is generally not possible with beta-particle emitters given achievable antibody specific activity, tumor cell antigen expression levels and the need to avoid prohibitive toxicity [1]; ten to 50 tracks through a cell nucleus are generally sufficient to sterilize a cell while thousands to tens of thousands of tracks are required for low LET radiation such as beta-particles or photons. Although the radiobiological properties of

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Delivery Systems for the Targeted Radiotherapy of Cancer".

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doi:10.1016/j.addr.2008.04.007

alpha-particles have been recognized since the early 1960s [2–9], their use in targeted therapy has been relatively recent. The first clinical trial of an alpha-particle emitter in radiolabeled antibody therapy employed ^{213}Bi conjugated to the anti-leukemia antibody, HuM195, and was reported in 1997 [10–12]. This was followed by a human trial of the anti-tenascin antibody, 81C6, labeled with the alpha-emitter, ^{211}At [13] in patients with recurrent malignant glioma. A number of reviews on alpha-particle emitters in targeted therapy have been published [1,14–17]. This review will concentrate on the dosimetry and relative biological efficacy of alpha-particle emitters. Results from recently reported clinical trials will also be summarized.

Absorbed dose is defined as the energy absorbed in a particular volume divided by the mass of the volume; it is the average energy density over a particular volume. Linear energy transfer or LET is a measure of energy deposition density along the pathlength of the particle. The LET of alpha-particles ranges from 25 to 230 keV/μm, depending upon the particle energy. This is 100 to 1000 times greater than the average LET of beta-particles. The much higher energy deposition pattern has the following two implications: 1. The physical quantity "mean absorbed dose" or average energy density, will not represent likely biological outcome in some circumstances. A microdosimetric analysis is then required to calculate a specific energy probability distribution [18]. 2. Per unit absorbed dose, the biological damage caused by alpha-particles is greater than that of beta-particles or other low LET radiations [19].

2. Dosimetry of alpha-particles for targeted therapy

2.1. Microdosimetry

The need for microdosimetry will depend upon the target size, the spatial distribution of alpha-particle emitters and the expected mean absorbed dose. Microdosimetry is typically required for alpha-emitter dosimetry resulting from accidental or occupational exposures or in the analysis of cell culture experiments involving low concentrations of alpha-emitting radionuclides. These are conditions in which a single track through the cell nucleus could, depending on its path, deposit a substantial fraction of the total energy absorbed by the nucleus. As outlined by Kellerer and Chmelevsky [20], microdosimetry should be used to evaluate likely biologic effect when the relative deviation of the average dose is greater than 20%. Roeske and coworkers [21–23] have developed simplified methods for microdosimetric analysis of such scenarios. Microdosimetric analysis typically provides the mean absorbed dose to targeted cells, the probability distribution of specific energy absorbed by targeted cells and the fraction of cells with zero energy absorption events (*i.e.*, alpha-particle traversals).

2.2. Conventional cell-level dosimetry

In most cases a microdosimetric analysis will not be necessary for targeted therapy applications because the activity level administered and mean absorbed doses to targeted cells are larger than in the cases described above and the resulting stochastic deviation is expected to be substantially less than 20%. In such cases standard dosimetry methods may be applied [24,25]. The standard approach to dosimetry calculations has been described by the Medical Internal Radionuclide Dose (MIRD) Committee [24]. In this formalism the absorbed dose to a target volume from a source region is given as the total number of disintegrations in the source region multiplied by a factor (the *S* value) that provides the absorbed dose to a target volume per disintegration in the source region. The sum of these products across all source regions gives the total absorbed dose to the target. MIRD cellular *S* values have been published for cell-level dosimetry calculations for situations in which the number of disintegrations in different cellular compartments can be measured or modeled [26]. Using these *S* values, the absorbed dose to the nucleus may be calculated from alpha-particle emissions uniformly distributed on the cell surface, in the cytoplasm or in the nucleus.

2.3. Whole-tissue dosimetry

The current methodology for estimating alpha-particle absorbed dose to a particular normal organ or tumor volume is based upon the assumption that all alpha-particle disintegrations in an organ volume deposit the alpha-particle energy uniformly within the organ and that the cross-organ dose from alpha-particle and electron emissions is negligible. The dose contribution from photon and electron emissions is calculated separately and added to the alpha-particle absorbed dose contribution which is scaled by the relative biological effectiveness (RBE). The methodology is described by the following equation:

$$D_t = RBE \cdot \frac{\tilde{A}_t}{M_t}(\Delta_\alpha \phi_\alpha) + \frac{\tilde{A}_t}{M_t}(\Delta_e \phi_e) + \tilde{A}_{wb} \cdot S^{\gamma}_{wb \leftarrow wb},$$

with:

D_t	absorbed dose to target tissue, t
$\tilde{A}_t$	total number of disintegrations in t
M_t	mass of target tissue
Δ_i	total energy emitted per disintegration by emission type, *i* (α = alpha, e = electron)
ϕ_i	fraction of energy emitted per disintegration by emission type, *i* that is absorbed in the target tissue.
$\tilde{A}_{wb}$	total number of disintegrations in the whole-body
$S^{\gamma}_{wb \leftarrow wb}$	whole-body photon absorbed dose per disintegration.

The total number of disintegrations in a particular tissue or in the whole-body, $\tilde{A}_t$ or $\tilde{A}_{wb}$, is typically obtained by longitudinal imaging, or counting tissue samples for radioactivity. Values for the Δ_i's are obtained from decay scheme tabulations that are published for each radionuclide [27]. The absorbed fraction for each decay type, ϕ_i, must be calculated from tabulations of absorbed fractions for the particular tissue geometry. In almost all cases, the absorbed fractions for alpha-particles can be assumed equal to 1; the absorbed fractions for electrons are likewise usually assumed equal to 1. The last term, adds the photon contribution to the target tissue from radionuclide disintegrations throughout the whole-body. A description of the methods used to calculate these values is beyond the scope of this review. Detailed methods are provided in Refs. [28–30]. Ref. [29], in particular, describes absorbed fractions that are tabulated by alpha-particle energy for bone marrow trabeculae. For alpha-emitters that decay via a branched decay scheme, as in ^{213}Bi, for example, (Fig. 1) it is important to account for the relative yield of each branch in determining the total energy emitted by each type of emission (*i.e.*, the Δ_i's). In the

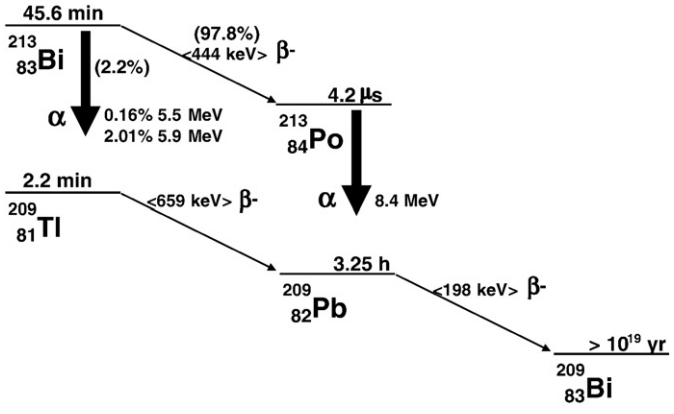

Fig. 1. Decay scheme for Bismuth-213.

Table 1
Electron emissions considered in the absorbed dose calculations; mean energy and range values are listed for beta emissions

Isotope	Electrons					
	Energy (keV)	Isotope % per disint.	Effective % per disint.	Mean energy (keV/disint.)	Δ_e (Gy kg/Bq s)	Elec. range (mm)
Bi-213	200	0.20	0.20	0.40	6.41E−17	0.5
Bi-213	347	2.55	2.55	8.85	1.42E−15	1.4
Bi-213	423	0.40	0.40	1.69	2.71E−16	1.9
Bi-213 (beta)	**444**	**97.80**	**97.80**	**434.23**	**6.96E−14**	2.1
Tl-209 (beta)	659	100.00	2.20	14.50	2.32E−15	4.2
Pb-209 (beta)	**198**	**100.00**	**100.00**	**198.00**	**3.17E−14**	0.5
Sum				657.67	1.05E−13	

The dominant contributors to electron absorbed dose are shown in bold.

case of ^{213}Bi, Tables 1 and 2 summarize the electron and alpha-particle emissions. The tables illustrate how to tally the total electron and alpha-particle energy. 2.2% of ^{213}Bi decays result in ^{209}Tl with the emission of an alpha-particle, the initial energy of the emitted alpha is either 5.5 or 5.8 MeV with the likelihood of each given by the yields shown on Table 2. In the remaining 97.8 decays, ^{213}Bi decays to ^{213}Po with the emission of a beta-particle. ^{213}Po, itself decays very rapidly via the emission of an 8.4 MeV alpha to ^{209}Pb which itself decays to ^{209}Bi with the emission of a 198 keV beta-particle. The exercise illustrates that a careful accounting of emissions is required in tallying the energy emitted per disintegration of the administered alpha-emitter, even when the decay scheme is relatively simple as for ^{213}Bi. Although outside the scope of this review, the photon *S* values (Table 3) can be calculated based on tabulations of photon absorbed fractions to different source-target organ combinations and photon energies [31].

3. Relative Biological Effectiveness (RBE)

3.1. RBE defined

RBE is calculated as the absorbed dose of a reference radiation (X-rays, or beta-particles of a particular energy), $D_r(x)$, required to produce a biological effect, x, divided by the absorbed dose of the test radiation, $D_t(x)$, required to produce the same biological effect:

$$\mathrm{RBE}(x) = \frac{D_r(x)}{D_t(x)}.$$

The RBE of alpha-particles, therefore depends upon the reference radiation and also, more importantly, upon the biological effect considered. RBE is used as a multiplicative term to adjust the estimated absorbed dose so that it reflects the likelihood or severity of a biological effect. If the biological end-point is stochastic such as cancer induction, then the RBE is approximately 20. In targeted therapy the relevant biological end-point is not carcinogenesis, but rather, efficacy or toxicity. Such therapeutic end-points are deterministic and the measure associated with them is not probability of occurrence (*i.e.*, risk) but severity of toxicity or level of response. The RBE for such end-points is in the range of 3 to 7.

Table 2
Alpha-particle emissions considered in the absorbed dose calculations

Isotope	Alpha-particles					
	Energy (keV)	Isotope % per disint.	Effective % per disint.	Mean energy (keV/disint.)	Δ_α (Gy kg/Bq s)	Alpha range (μm)
Bi-213	5549	0.16	0.16	8.88	1.42E−15	42.0
Bi-213	5869	2.01	2.01	117.97	1.89E−14	45.5
Po-213	7614	0.003	0.003	0.22	3.58E−17	66.0
Po-213	8375	100.00	97.80	8190.75	1.31E−12	75.6
Sum				8317.82	1.33E−12	

Table 3
Individual photon *S*-factors and summed photon *S*-factor used for ^{213}Bi photon dosimetry [25]

Isotope	Photon energy (keV)	*S*-factor (Gy/MBq s)
Bi-213	440	5.78E−11
Bi-213	79	9.84E−13
Tl-209	117	1.60E−12
Tl-209	467	6.71E−12
Tl-209	1566	2.37E−11
Sum = $S_{wb\leftarrow wb}$		9.08E−11

3.2. RBE, Q and w_R

RBE is occasionally confused with quality factors. This confusion reflects the historical evolution of RBE which was originally defined as Relative Biological Efficiency and intended to apply to both radiobiology (deterministic effects) and protection (stochastic effects). As currently recommended by the International Commission on Radiological Protection (ICRP), RBE is not to be used directly in radiation protection but only as a starting quantity to derive the quality factor, *Q*, and the radiation weighting factor w_R. The RBE values used in their derivations apply to stochastic events such as cancer induction rather than deterministic or acute events such as toxicity and tumor cell sterilization in cancer therapy patients. ICRP Quality and weighting factors are derived from animal experiments and from analysis of historical alpha-emitter exposures. In contrast to RBE values, weighting factors are not directly measured values but rather the recommendations of the International Commission on Radiological Protection [32].

RBE and, *Q* or w_R, are unit-less factors that convert absorbed dose (in units of Gray (Gy)) to an absorbed dose equivalent which is referred to by the special name, Seivert (Sv). The Seivert is not a unit in the conventional sense, but rather, is intended to indicate that the dose value has been adjusted to reflect a biological risk that is associated with stochastic effects. Although the product of RBE and absorbed dose in Gy is conventionally referred to as a Sievert, this is not strictly correct since Sievert should only be used to designate the risk of incurring stochastic biological effects such as cancer. No special name has been chosen to reflect a dose value that has been multiplied by an RBE and that specifically reflects the severity of a possible acute effect. Until the appropriate regulatory bodies establish a means of distinguishing these two effects explicitly it will be important to note whether a value in Sv is for protection (stochastic effects) or for evaluation of toxicity and anti-tumor efficacy (acute or deterministic effects).

4. Clinical trials of targeted alpha-particle emitters

Clinical trials of alpha-particle emitters have demonstrated the expected hallmarks of targeted alpha-particle emitter therapy — anti-tumor efficacy with minimal toxicity. The ^{213}Bi Phase I/II trials against acute myeloid leukemia (AML) demonstrated complete responses in patients whose tumor burden had been previously reduced by cytarabine. The responses in this very high risk population lasted up to 12 months. Myelosuppression was tolerable and no significant extramedullary toxicity was observed [33,34]. In addition to this, there are also on-going trials in Europe and Australia. These trials are investigating targeted ^{213}Bi against lymphoma, progressive glioma, and melanoma [35–38]. Median survival in recurrent malignant brain cancer patients following administration of ^{211}At-labeled anti-tenascin antibody into the surgically created tumor resection cavity was

increased from the historically expected 25 to 30 weeks to 54 weeks [39]. As of the last review of these data in 2004, two patients with recurrent glioblastoma were alive 151 and 153 weeks after ^{211}At-labeled chimeric 81C6 therapy [40]. Clinical investigations in humans, using Ra-223 for therapy of painful skeletal metastases in prostate and breast cancer patients, showed a strong and consistent reduction in alkaline phosphatase levels [41,42]. In a large fraction of prostate cancer patients, this was accompanied by reduced prostate-specific antigen relative to baseline. Myelosuppression was minimal and thrombocytopenia was not dose-limiting.

The alpha-emitting radionuclide, ^{225}Ac has a decay scheme that includes 3 alpha-particle emitting daughters. The last alpha-emitting daughter in the series is ^{213}Bi. The cytotoxicity of this in vivo isotope generator or "nanogenerator" is 1000 times more potent than ^{213}Bi, *in vitro*, and has demonstrated remarkable efficacy in pre-clinical studies [43]. In a first-in-human phase I dose escalation study of this nanogenerator, AML patients treated with a single infusion of 23 to 170 μCi (0.5 to 2 μCi/kg) have demonstrated dose-related reduction in peripheral blood and bone marrow blasts with no acute or delayed toxicity at 10 month follow-up [44]. Accrual to this trial continues.

5. Future prospects

Targeted radionuclide therapy using beta-emitting radionuclides such as iodine-131 (^{131}I) and yttrium-90 (^{90}Y) has been investigated over the past 20 years. The fundamental advantage of this modality over external beam is that the radiation may be delivered to individual targeted cells from within. Targeted alpha-particle therapy introduces the additional advantage of delivering a radiation type that is more potent than that used in external beam or targeted radionuclide therapy. The clinical trials performed to date have shown efficacy with minimal toxicity. The major limitation to widespread implementation of this therapy is the limited and therefore costly radionuclide supply. As this is addressed by infrastructure investments and technological advances, the challenge will be to package delivery of targeted alpha-emitter therapy so that the high level of multidisciplinary expertise needed to deliver such therapy today becomes unnecessary in the future.

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