Review

Radioimmunotherapy of malignancy using antibody targeted radionuclides

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Summary Antibodies directed against tumour associated antigens provide a means for delivering preferentially cytotoxic radionuclides to the cells of primary and secondary tumours. The factors that influence the effectiveness of the radiation in the tumour compared with its effect on the radiosensitive normal tissues include the specificity of the antibody, the distribution of targeted energy within the tumour and the host's response to the injected foreign antibody. Recently some encouraging results from clinical trials of radioimmunotherapy have been reported in the literature. There is a continual search for more avid and specific antibodies, and the techniques of genetic engineering are being applied to the problem of reducing the antigenicity and mass of the carrier antibody. The improved efficiency of the labelled antibody needs to be supplemented by an identification of those tumours most likely to respond to this form of therapy.

There is growing interest in the possibility of treating disseminated malignant disease by antibody-targeted cytotoxic radionuclides. The impetus for this comes from three sources. First, the introduction of monoclonal antibodies (McAbs), which allows more precise targeting than has been possible with polyclonal antibodies. Second, the improved gamma and positron tumour immunomaging that can be obtained with McAbs has illustrated clearly that radionuclides can be concentrated in tumours. Third, there have been a number of reports indicating clinical response to antibody-targeted radionuclides (Order et al., 1980a 1985; Carrasquillo et al., 1984). Order and his colleagues at the Johns Hopkins Hospital, Baltimore, have been using radiolabelled polyclonal antibodies as a part of their treatment of carcinoma of the liver (hepatocellular and cholangiocarcinoma) for some years, and have reported clinical responses with radiation/drug regimens which include $^{131}$I-labelled anti-ferritin and anticarcinoembryonic antigen (CEA). Using the same isotope of iodine, attached to a murine McAb against p97, an oncofoetal glycoprotein of human melanoma, Carrasquillo and his colleagues (1984) have reported clinical regression in malignant melanoma.

The stage would now seem to be set for significant advances in this field. It is a technically complex form of therapy requiring a multi-disciplinary approach, calling upon immunologist, clinician, radiochemist, radiobiologist and physicist alike. In this review we shall examine in turn the target, the carrier and the radionuclide 'warhead' and finally comment upon the problems and possibilities of this form of treatment.

Target

The target for the administered ionizing radiation is the DNA of the malignant cells — or more particularly the DNA of the malignant 'stem' cells. The sterilizing effect of radiation is thought to be due predominantly to the induction of double strand breaks (DSB). From in vitro studies with Ehrlich ascites tumour cells Blöcher (1981, 1982) found that for low Linear Energy Transfer (LET) radiation (photons, electrons) an average of ~200 DSB is required per cell to sterilize ~99% of a tumour cell population. For high LET radiation ($\alpha$ particles) it is likely that somewhat fewer DSB are required.

One advantage that targeted radiation has over antibody targeted toxins is that a tumour cell without the appropriate antigenic determinant can yet be sterilized by the radiation cross-fire from adjacent cells having the determinant and binding the labelled antibody. The sterilizing efficiency of the cross-fire effect will depend to a large degree upon the spatial arrangement of the malignant 'stem' cells with respect to the labelled carrier antibody. We know from immunohistochemical

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studies of human tumour biopses that many of the McAbs directed against tumour-associated membrane antigens will attach to the surface of only a proportion of the malignant cells (antigenic heterogeneity) (Burchiel et al., 1982; Wright et al., 1983; Edwards et al., 1985; Fargion et al., 1986). Foster et al. (1982a,b) have observed such heterogeneity of antigenic expression in primary breast cancer and the associated lymph node metastases using a McAb to human milk fat globule membrane (HMFG). They also observed antigenic heterogeneity within the different cell types of normal breast tissue. Wright et al. (1983) examined human prostatic carcinomas, both primary and secondary tumours, using a specific anti-prostatic carcinoma McAb and recorded the distribution of antigen as being either in a patchwork in which the binding and non-binding cells seemed to alternate, or one in which large areas of tumour devoid of binding sites alternated with high binding areas. Antigenic heterogeneity has been observed in a number of other human tumours (Hand et al., 1983; Natali et al., 1983), and on cultured human cells (Albino et al., 1981; Burchiel et al., 1982) and has variously been associated with heterogeneity of cell size (Burchiel et al., 1982) cell function (Foster et al., 1982a), stage of cell cycle (Burchiel et al., 1982; Kufe et al., 1983) and invasiveness (Suter et al., 1985).

Whatever the explanation(s) of antigenic heterogeneity there seems to be little doubt that in many tumours it will result in a very uneven distribution of targeting antibody. The cross fire effect will in part compensate for this. It is also possible that polyclonal antibody can reduce the unevenness. Otherwise the solution may be in the use of McAb ‘cocktails’ (Natali et al., 1983; Carrasquillo et al., 1984). Another possibility is the use of biological response modifiers (BRM) to increase antigen expression. Recently, Greiner and his colleagues (1984) illustrated an increase in the expression of tumour associated antigenic determinants, both cell membrane density and the number of cells expressing the antigen, when human breast or colon carcinoma cells were cultured in the presence of the BRM recombinant human leukocyte α-interferon.

Edwards (1985), in his excellent review of antigenic heterogeneity in tumours, suggested that there may be less heterogeneity associated with protein rather than carbohydrate determinants and that we should be examining more carefully McAbs to the protein portion of cell membrane glycoproteins. In their work with human melanoma cell lines Burchiel et al. (1982) observed that antigenic heterogeneity appeared as a range of concentration of antigen, rather than an ‘all or none’ situation. If this reflects the in vivo position it would indicate that many of the cells in a tumour may still bear tumour-associated antigen, but in low concentrations. Under such circumstances a high degree of cell sterilization could still be achieved, and cells with few binding sites killed, if the radioactivity were to be delivered by small numbers of antibody molecules heavily laden with a β emitter. The alternative is to use an α emitter (not more than one atom per molecule), or a radionuclide that decays by electron capture and/or internal conversion in which prolific emission of low energy (Auger) electrons occurs. In the latter case, as Auger electrons have ranges predominantly of <1 µm, a mechanism would have to be found for positioning the radionuclide in close proximity to the DNA of the target cell (Hofer, 1980), vide infra.

Carrier

The purpose of the carrier antibody is to deliver to the disseminated tumour cells sufficient radioactivity to sterilize them. Although attention is naturally focussed on delivering high levels of activity as quickly as possible to the tumour it is equally important that the retention time of the radionuclide in the tumour relative to that in the dose-limiting normal tissue should be for as long as possible (DeNardo et al., 1982). To maximise the ratio of tumour to non-tumour dose we support the view of DeNardo et al. (1983) that the physical half-life of the radionuclide should be similar to the biological half-life of the carrier antibody in the tumour. Unfortunately, the latter half-life is not easily measured, but can be expected to vary greatly from one tumour to the next (Leichner et al., 1983; Rostock et al., 1984; Klein et al., 1985). Larson et al. (1983) have reported an effective half-life (composite of biological and physical half-lives) of 46 h in melanoma following injection of a patient with 131I-labelled Fab fragments of an anti-melanoma McAb. Using 131I-labelled antiferritin polyclonal antibody, Leichner and his colleagues (1983) reported effective half-lives within the patient’s primary hepatoma of between 0.25 and 7.8 days – depending upon the method of purification and the subsequent diluent of the administered antibody.

The documented positive clinical response to targeted radiation has been almost entirely with polyclonal antibody as carrier (Order et al., 1980a; 1981). In order to give repeated injections of labelled targeting antibody and avoid patient sensitization to foreign antibody these authors used polyclonal antibody from a different species for each injection (Order et al., 1985). There has not been sufficient time for a realistic clinical assessment of the value of McAbs in radioimmuno-therapy (RIT); however, it would seem that the more specific targeting potentially obtainable with
McAbs should offer an improvement over polyclonal antibodies. There is as yet no clinical evidence for the increased value as carrier of enzyme-digested fragments of Ig above the parent molecule. However, the experimental evidence so far points to a distinct advantage in the use of such fragments (DeNardo et al., 1983; Buraggi et al., 1985). The preparation of F(ab')2 fragments removes the problem of Ig binding to Fc receptors in the liver which otherwise produces a rapid and wasteful accumulation of radionuclide in that organ (Buraggi et al., 1985). The use of Fab and similar univalent fragments should prevent antigenic modulation and the associated fall-off in retention by the tumour cells of injected antibody (Glennie & Stevenson, 1982; Cobbold & Waldmann, 1984). On the other hand antibody fragments may be less well retained by the tumour and therefore the radiation dose to the tumour cells reduced.

The factors controlling the loss of antibody or antibody fragment from the tumour and its intra- and extra-tumour catabolism are ill understood. There is however clear evidence from both human and animal systems that antibody fragments are more rapidly cleared from the body than is the parent immunoglobulin (Ig) (Buraggi et al., 1985).

No one has been surprised to find that the administration of xenogeneic antibody produces on the first or subsequent injection an immune response by the patient to the foreign protein (Primus et al., 1980; Carrasquillo et al., 1984). What has perhaps been surprising is the amount of foreign antibody that can be injected. Meeker and his colleagues (1985) were able to inject into patients with a minimum of side effects 40–400 mg of mouse McAb on 6–9 occasions over 3 weeks to totals in excess of 3000 mg. The response by patients to foreign antibody may in time be circumvented, or at least greatly reduced, by the use of human monoclonal antibody (Sikora et al., 1985). Additionally, recent advances in genetic engineering now make it possible to prepare human Ig with high avidity rodent variable regions. Sahagan et al. (1986) have shown that murine variable and human constant region exons can be fused to produce 'chimaeric' immunoglobulin γ and κ genes and that these constructs when co-transfected into murine myeloma cells can secrete intact, functional, antibody. These cells when grown as an ascites in mice produce antibody with similar specificity for epitopes on human tumour cells as the parent murine McAb.

Complexes formed from the injected, labelled, foreign (antigenic) antibody and the host (reactive) antibody can accumulate in the reticuloendothelial system (RES) and kidneys producing a harmful radiation dose. In a similar way immune complexes formed from circulating tumour antigen and injected (labelled) specific antibody will increase the radiation dose to the RES and kidneys at the expense of the tumour dose (Dillman et al., 1984). The problem of circulating tumour antigen is well recognised (Nadler et al., 1980; Warenius et al., 1981; Hagan et al., 1983). Unfortunately it remains a significant stumbling block in RIT. In B cell tumours, where the labelled antibody is commonly directed against the idiotype of the antibody secreted by the tumour cell, some reduction in circulating antigen (lymphoma-secreted antibody) can be obtained by plasmaphoresis, but the reduction is short-lived (Hamblin et al., 1980; Meeker et al., 1985).

It can be argued that once a tumour has taken up a significant amount of labelled antibody there is an advantage in then clearing the blood of residual circulating antibody in order to reduce the irradiation of the sensitive normal tissues, e.g., bone marrow. Begent and his colleagues (1982, 1984) have shown that significant clearance can be achieved by using a second antibody directed against the first (labelled) antibody which leads to the sequestration of the labelled antibody in the spleen and liver. The advantage thus gained from protection of the particularly radiosensitive tissues needs to outweigh the disadvantage from the accelerated clearance of antibody from the tumour that results from a lowered level of circulating antibody. It is also important that the RES itself is not seriously damaged by the sequestrated labelled antibody.

One of the factors that will control the speed of uptake of antibody by the tumour is the ease with which the antibody can cross the capillary wall. We know that in normal tissues the permeability of capillaries varies between organs and in those organs with fenestrated capillaries (e.g. thyroid, bone marrow, renal glomerulus, liver, spleen, choroid plexus) there is a very rapid passage of macromolecules. If malignant cells originating from these tissues should stimulate the host organ to produce similarly fenestrated capillaries for their support these tumours might be good candidates for RIT. Ludatscher et al., (1979) in an ultra-structural study of follicular carcinoma of the thyroid have indeed shown fenestration of the tumour capillary bed. In a similar examination of brain metastases from carcinoma of the kidney, Hirano and Zimmerman (1972) have reported the formation of fenestrated capillaries to support the infiltrating cell population.

**Radionuclides**

Satisfactory tumour localization can be obtained in experimental animals using specific antibodies...
variously labelled with $^{109}$Pd (Fawwaz et al., 1984), $^{131}$I (Goldenberg et al., 1981; Zalcberg et al., 1984; Badger et al., 1985), $^{90}$Y (Hnatowich et al., 1985) and $^{211}$At (Vaughan et al., 1982; Bateman et al., 1983); but only $^{131}$I has so far been used clinically. Much of the clinical work in this area has been carried out by Order and his colleagues (Eitinger et al., 1979; Order et al., 1980a; Order et al., 1981; Leichner et al., 1984). They have reported a significant response in hepatocellular carcinoma to $^{131}$I-anti-ferritin, and by biliary tract carcinoma to $^{131}$I-anti-CEA, when used as part of a complex drug/radiation regimen. They believe that the radiation plays a significant rôle in the regimen. Carrasquillo and his colleagues (1984) have used $^{131}$I-labelled McAb directed against the p97 antigen in melanoma patients and record some beneficial response. Courtenay-Luck et al. (1984), Epenetos et al. (1985) and Pectasides et al. (1986) have reported a degree of success with locally injected $^{131}$I-labelled anti-HMFG and anti-epidermal growth factor receptor. These workers injected the labelled McAb either directly into the tumour infiltrated body cavity or into the artery supplying the tumour.

Iodine-131 has, over many years, proved its tumour destructive capacity in thyroid carcinoma and it was therefore natural to use this radionuclide for antibody-targeted therapy. It has the additional advantages that the chemistry of antibody labelling is well researched and the radionuclide is relatively cheap. However, the variation in the pattern of distribution of malignant stem cells within the tumour mass, the variation in diameter of primary tumours and their metastases and the different retention time of different antibodies makes it unlikely that any one radionuclide will be suitable on all occasions.

As we have observed above, one therapeutic approach to the problem of a low number of binding sites per tumour cell is to use a radio-label with high cytotoxic efficacy. The $\alpha$-particle emitting radionuclides fall into this class and a number of research groups are pressing the case for the use of $\alpha$ emitters in RIT (Vaughan et al., 1982; Harrison & Royle, 1984; Kozak et al., 1986). Harrison and Royle (1986) have shown that astatine-211 labelled McAb can cure early T cell lymphoma in mice, and Kozak and his co-workers (1986) have reported that in vitro bismuth-212 labelled anti-Tac greatly reduces the proliferative capacity of a human T cell lymphoma line. The number of suitable $\alpha$ emitters is small but bismuth-212 (T (half-life) = 1 h) may be induced in situ by administering the parent lead-212 (T = 10.6 h) which decays by $\beta$-emission to the $\alpha$ emitting daughter bismuth-212 and its daughter polonium-212 (T = 304 ns). Although $\alpha$ particles are very efficient in sterilizing tumour cells it should be remembered that they will be equally efficient in sterilizing many normal cells – and that while with $\beta$ emission fractionation of treatment allows time for normal tissues to repair, such repair does not follow $\alpha$ particles irradiation. An advantage of $\alpha$ particles which may be important with some tumours is that the protective effect of hypoxia seen with $\beta$ radiation does not occur.

There are other decay processes, namely electron capture and internal conversion, that can result in even more local energy deposition effects than $\alpha$ emission. Both electron capture and internal conversion result in the removal of an inner shell orbital electron from the atom, usually in the K-shell. This introduction of an inner shell vacancy into the atom initiates a cascade of electron transitions which can result in the emission of a number of very low energy Auger electrons of the order of a few keV or fraction thereof whose ranges can span from a few nanometres to a few micrometres. The prolific emission of Auger electrons from $^{125}$I has been shown to be extremely effective when it is incorporated directly into the DNA using the thymidine precursor iododeoxyuridine (Burki et al., 1973; Feinendegen, 1975; Liber et al., 1983). Because of the short range of most Auger electrons the effectiveness in cell inactivation of sources like $^{125}$I or $^{118}$Sb is mostly lost when they are not bound to, or sited within, a few atomic spaces of the DNA (Hofer, 1980).

The problem is to introduce these Auger emitters preferentially into the DNA helix of the tumour cells. In their study of $^{123}$I-labelled DNA intercalating substances Martin and his co-workers (Martin, 1977; Martin et al., 1979) have shown how effective these labelled compounds are at producing DSB. Working in a different but related area Diener et al. (1986) have shown specific sterilization of T lymphocytes in vitro using a cytotoxic DNA intercalating drug (daunomycin) linked to a T cell specific McAb. After internalization of the antibody-daunorubicin conjugate the drug was uncoupled in the lysosomes by the dissociation of an acid sensitive aconityl linkage. There would seem to be a future for labelling such DNA intercalating agents with Auger emitters and linking them to specific McAbs so that they would be preferentially introduced into tumour cells, and not bone marrow and other sensitive tissues – and the intercalating agent would subsequently introduce the Auger emitter into the tumour cell DNA helix.

Normal tissues

In focussing attention on methods for increasing the deposition of energy in the tumour it is essential that a similar increase does not occur in the energy
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deposited in the bone marrow or other critical tissue. In clinical practice this problem is tackled by experience gained from monitoring of haematological and blood biochemical parameters during and after therapy.

The most informative clinical toxicology yet available comes from the clinic and laboratories of Dr S.E. Order. For example, 14 patients were evaluated during the treatment of primary liver cancer with $^{131}$I-labelled polyclonal antibody (Ettinger et al., 1982). The 14 patients received activities between $1.4 \times 10^9$ Bq and $5.8 \times 10^9$ Bq of $^{131}$I and the main toxicity was to bone marrow. Seven of the 14 patients had severe life-threatening leukopenia and thrombocytopenia. The lowest activity of $^{131}$I to produce severe haemotoxicity was $3.4 \times 10^9$ Bq which gave absorbed doses to the total body, liver and tumour of 1.4, 6 and 19 Gy respectively. This patient had a partial tumour response. The next highest injected activity ($3.7 \times 10^9$ Bq $^{131}$I), which was without effect on the tumour, gave total body, liver and tumour absorbed doses of 1.1, 4 and 15 Gy. In this case there was no bone marrow toxicity but there was a transient rise in certain circulating hepatic enzymes. These results with polyclonal antibody can be compared with those of Larson et al. (1983) where they treated malignant melanoma with $^{131}$I-labelled Fab fragments of McAb IgG seeing p97, an oncofoetal glycoprotein of human malignant melanoma. The administration of $3.7 \times 10^9$ Bq $^{131}$I resulted in an absorbed dose to bone marrow, liver and tumour was 0.3, 3 and 10 Gy respectively. They considered the bone marrow to be the critical organ and reported leukopenia and thrombocytopenia at a cumulative activity of $\sim 2 \times 10^{10}$ Bq $^{131}$I. These authors stressed that a large variation between patients in tissue absorbed dose can be expected, due in part to differences between preparations of $^{131}$I-labelled antibody and in part to the interaction of the antibody and the patient. It should be remembered that when comparisons of dose-effects are being made the period of time over which a dose is absorbed has to be taken into consideration as does the fractionation regimen – as they both have a bearing on tissue repair.

It is a common finding in gamma scintigraphy that the radionuclide accumulates extensively in the liver and spleen. Not only can this interfere with the interpretation of the scan but also it indicates that with the higher activities used in therapy the dose-limiting radiotoxic effect may be to these organs rather than to the bone marrow (Ettinger et al., 1982; Frank et al., 1983). In other circumstances the kidney could be the normal tissue most affected. This may arise from localization of radiolabelled immune complexes or Ig fragments, or because use is being made of a radioisotope of an element that concentrates in the kidney. For example, $^{109}$Pd-labelled anti-melanoma McAb is seen to give rise to the accumulation of $^{109}$Pd in the kidney of experimental animals (Fawwaz et al., 1984). There is an isotope of mercury with potential therapeutic value ($^{197}$Hg) but this element can be retained by the proximal convoluted tubules of the kidney. Where this is any suspicion of the accumulation of a radionuclide in a confined area within an organ, e.g., a particular cell type, estimations of the local absorbed dose and not simply the absorbed dose to the whole organ should be made.

Prospects for radioimmunotherapy

The treatment of cancer with targeted radionuclides (zetatherapy=$\zeta$ to treat by seeking out; $\zeta\tau\varepsilon\alpha\omega$ = to seek out) is an area of radiotherapy that with our present state of knowledge appears to have considerable potential. For this potential to be realised there are problems that need to be addressed and resolved.

(i) Antigenic heterogeneity The erratic distribution of binding sites throughout a tumour is likely to produce a similarly erratic deposition of energy in the tumour cell population. There are a number of approaches being adopted to try to achieve a more uniform radiation dose. In the foreseeable future it would appear that success is most likely to come from the use of a combination of McAbs directed against different epitopes or from the production of new McAbs to less heterogeneously distributed tumour-associated antigens.

(ii) Specificity of antibody Many of the presently available antibodies localize in areas other than the tumour. It is important that the search continues for carriers that will preferentially localize in tumours.

(iii) Fractionation of radiation With external irradiation fractionation of the dose is used to give the normal tissues time to repair. The same principle will apply with $\beta$ emitters – but not with $\alpha$ emitters, and probably not with Auger cascades. The difficulty with fractionation of the dose with RIT is that at present we have the major problem of the antigenicity of the carrier. The pragmatic and seemingly successful approach to this problem made by Order and his colleagues (1985) has been to use a succession of polyclonal antibodies raised in different species of animal. An obvious alternative is to employ genetic engineering to build carrier molecules with a minimum of antigenicity – although we are still left with the antigenicity of the idiotype. In the more distant future we may be able
to approach the problem by blocking either the patients' recognition of the foreign antibody or the ability to respond to it.

(iv) Access of antibody to target antigen  An estimate can be made of the radioactivity in a tumour mass using scintigraphy or positron-emission tomography. This does not however provide information on the microscope distribution of activity, which is essential before any estimate can be made of the proportion of tumour cells likely to be sterilized or give advice on the most appropriate radionuclide. This information can only be obtained from biopsies of the tumour in the days following the injection of labelled antibody – and such material is rarely available. This represents a major gap in our knowledge. We can make the assumption that the capillaries in a rapidly growing tumour will be relatively permeable to antibody – but such may not be the case in the common slow growing tumours, and we may need to seek ways for improving tumour capillary permeability. Efforts are continually being made to reduce the size of the carrier molecule in an attempt to improve access to extravascular sites. The molecule shape and charge need also to be considered.

As with all new forms of tumour therapy the initial optimism will become tempered with experience. Our aim must therefore be to try to identify as quickly as possible those categories of patients who will benefit by the inclusion of RIT in their treatment regimen.

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