Radiolabeled Antibodies: Results and Potential in Cancer Therapy

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Abstract

Radiolabeled antibodies are analyzed from the classical approach in radiation oncology being compared to geometric isotopic implants, external radiation, and tumor-dose response and energy of the isotope used for cytotoxicity. In addition, physiological factors that limit antibody uptake, varied routes of administration, toxicity of treatment, as well as present clinical progress are reviewed.

Introduction

To consider the use of radiolabeled antibodies in cancer therapy requires a fundamental understanding of physics-dosimetry, radiobiology, and the known potentials for response in varied cancers.

Radioactive Implants

Standard Techniques. Classical implantation experience with radium or iridium has shown 40–60 rads/h to be the standard therapeutic dose for head and neck cancers and for gynecological cervical and uterine cancers (1, 2). Such physical implants with seeds or needles yield 1000–1400 rad/day and, in combination with 4000–5000 rad external radiation, have been associated with tumor regression (1, 2). Tumor regression has also been observed with total applied tumor doses of 6000–8000 rad from implants alone (1, 2). Reduced dose rates, below 25 rad/h, require increased total tumor dose to achieve similar tumoricidal effects.

Low Dose Rate. Low dose rate radioactive implants require longer radiation times for numerical doses equivalent to standard doses. For example, 3000 rad at either 5 or 60 rad/h requires 600 h compared to 50 h. Prolonged irradiation times seem to cause some tumor cells to shift to G2 and M phases of the cell cycle, where they are more radiosensitive (3). Low dose rate irradiation also amplifies the cytotoxicity of cis-diamminedi-chloroplatinum(II) when used in combination with that chemotherapy agent (4). Low doses of Adriamycin used in combination with low dose rate irradiation also appear to shift tumor cells into the G2 and M phase of the cell cycle (3).

Dose Response

Consideration must be given to the known dose-response data related to external radiation and solid tumor remission so that realistic expectations with regard to response in radiolabeled antibody therapy can be made. Solid tumors such as non-Hodgkin's lymphocytic malignancies (3000 rad/3 weeks) (1), Hodgkin's disease (4000 rad/4 weeks) (5), colorectal cancer (5000 rad/5 weeks) (6), minimal residual disease head and neck cancers (5000 rad/5 weeks) (1, 2), and active head and neck cancers (6000–9000 rad/6–9 weeks) (1, 2) have defined dose-response criteria. In addition, boost doses of radiation in these programs often use radioactive needles or seeds. The use of radiolabeled antibody is a biological method of radioactive implantation rather than a physical method. In addition, the dose rates and the total dose are reduced with radiolabeled antibody therapy (7).

The type of radiation emission, its range, the tumor dose rate, and the total tumor dose are important considerations for selecting a radioisotope to link to an immunospecific antibody for radioimmunotherapy. These features of radiolabeled antibody depend not only on the isotope but also on the ability of the antibody to target the tumor and to deposit in a significant concentration. Finally, the circulating radioimmunoglobulin must also be evaluated for its potential normal tissue or organ toxicity.

β-Irradiating isotopes such as 131I, 90Y, and 186Rh allow radiolabeled antibody application for relatively radiosensitive tumors or, when integrated with chemotherapeutic drugs, for relatively radioresistant tumors. Experience to date has demonstrated 131I-labeled antibodies to yield 5 rad/h and total tumor doses of 1000–1500 rad in hepatic cancer, while 90Y has been demonstrated to yield 15 rad/h and tumor doses of up to 2700 rad in treatment of Hodgkin's disease (7, 8). Obviously, the tumor antibody concentration, the labeling index of isotope to antibody, the number of sequential infusions, the tumor effective half-life of the isotope, and other factors combine to determine the dose rate and total tumor dose.

Effective radiolabeled antibody therapy requires selection of an isotope able to deliver an adequate dose rate and total tumor dose. For example, the higher dose observed when 90Y is substituted for 131I is increased a partial remission rate of 40% with 131I in Hodgkin's patients who failed MOPP-ABVD (9) to complete remission with 90Y in the same patient population (10). The most dramatic complete remission using 90Y occurred in a Hodgkin's patient failing chemotherapy who had bilateral axillary and hilar nodes, a mediastinal mass, and a left chest wall and left breast mass (8). A single dose of 30 mCi 90Y antiferritin led to complete remission; 16 days later autologous bone marrow infusion led to ultimate hematopoietic restoration. Analysis of remission included physical examination, magnetic resonance imaging, and computer axial tomography. This patient remains in complete remission 4 months following radiolabeled antibody therapy. Similar results have been achieved in several other patients and should be achievable, ultimately, in non-Hodgkin's disease as well with anti-pan-B or with antidiotype antibodies.

Hepatocellular cancer is not treatable to high doses with external radiation due to the limit of normal liver toxicity. Hepatocellular cancer has been observed to respond to the low dose rate of 131I-antiferritin when this radiolabeled antibody is integrated with modest doses of Adriamycin (15 mg) and 5-fluorouracil (500 mg) (11). Recent laboratory data have indicated that Adriamycin shifts tumor cells into a more radiosensitive cell cycle phase, making low dose rate irradiation more cytotoxic (3). Most recently, in a randomized study to be published, the conversion of hepatocellular cancer to surgical resectability, as well as preferential partial remission in AFP-hepatocellular cancer, has been observed (7, 11, 12).

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The abbreviations used are: MOPP-ABVD, mechloretamine, oncovin, procarbazine, prednisone-adriamycin, bleomycin, vincristine, dacarbazine; AFP, α-fetoprotein.
Protocols that recognize defined objectives in malignancies where either dose-response or drug integration would indicate potential success are fundamental to the future clinical success of \( \beta \)-emitting isotopes linked to antibody. Attempts to gain remission in relatively radioresistant tumors such as melanoma with radiolabeled antibody may not be realistic if the dose requirements for these tumors cannot be met (13). In such tumors drug integration or higher tumor dose deposition are needed. Until investigators appreciate the known radiobiology of potential therapeutic administration remain unknown. Early work regarding anti-epidermal growth factor with \( \text{I}^{131} \) indicates the potential for remission in glioma and perhaps other tumors with this combined therapy (15).

Isotopes such as Auger electron emitting \( \text{I}^{131} \) and \( \alpha \)-emitting \( \text{Bi}^{212} \) depend upon internalization or surface proximity of the radiolabeled antibody (15). Both the dosimetry of such irradiation and the radiobiology of potential therapeutic administration remain unknown. Early work regarding anti-epidermal growth factor with \( \text{I}^{131} \) indicates the potential for remission in glioma and perhaps other tumors with this combined therapy (15).

Other Isotopes

Chelate Domination

In hepatocellular cancer the remaining highly active normal liver has shown such an attraction for the chelate that it dominated the Fab end in targeting which caused more accumulation of the antibody in the normal tissue than in the tumor (18). We have termed this phenomenon "chelate domination." These same patients, however, could be targeted with the same antibody linked to \( \text{I}^{131} \) with significant tumor deposition and minimal normal liver dose. Interestingly, chelate domination does not seem to occur on Hodgkin's disease where the same chelated antibody is successful in targeting and remitting the tumors (8). We anticipate the development of better chelates that may allow excretion of nonbound chelated antibody.

Factors Limiting Antibody Uptake

Neovasculature. The quantity of neovasculature is prominent among the factors that limit antibody uptake. Studies with \( \text{I}^{131} \)-antiferritin having equal ferritin content in equal sized tumors in four rodent hepatomas with unequal neovascularization showed that tumor targeting by the radiolabeled antibody was determined by vascular content (19). Hyperthermia has been shown to increase vascular permeability both in tumor and normal tissue (20). New data from the laboratory and the clinic indicate that preirradiation with modest doses of 600–900 rad increases vascular permeability in the tumor but not in normal tissues (21).

Interstitial Pressure. Very little is presently known about the interstitial pressure in clinical situations, but experimentally interstitial pressure reduces the influx of radiolabeled antibody (22).

Antigen Exposure and Modulation. Antigen exposure and modulation remain minimally described. Antigenic modulation is best known in the TL+ system experimentally, or clinically in T101 (23, 24). Although antigen exposure has not been described to any great extent, antigen content does not equal antigen exposure; i.e., the latter indicates antigen available for immunospecific antibody binding. In our own experience, ferritin is synthesized and secreted by malignant cells, resides in the stroma, and is most dense at the perivascular region. The maximum radiolabeled antibody binding occurs in the perivascular region; less antibody binding occurs at the other sites due to presumed maximum antigen-antibody concentration.

Isotope Antibody Linkage

Other major obstacles to be overcome by radiolabeled antibody cancer therapy include antibody linkage, antibody deposition, route of administration, immunogenicity, and normal tissue toxicity. In labeling with \( \text{I}^{131} \) our experience has not shown significant differences between lactoperoxidase, Bolton Hunter, or chloramine-T methods. The major problem with \( \text{I}^{131} \) has been the ease of dehalogenation of \( \text{I}^{131} \)-monoclonal antibodies (16). Polyclonal antibodies may be selected by species, e.g., rabbit, pig, baboon, to avoid such dehalogenation (16). Dehalogenation is clinically observed when total isotope dose falls rapidly, usually within 24 h, when a significant amount of \( \text{I}^{131} \) appears in the urine, and when tumor targeting is not observed at 24 h. Simple whole body counts at a distance of 1 meter indicate substantial loss of radioactivity, and a nuclear scan will show radioactive secretion in the stomach and small intestines.

The chelation of \( \text{In}^{111} \) and \( \text{Y}^{90} \) are similar (8). \( \text{In}^{111} \) is the \( \gamma \)-emitting isotope used for diagnostic scanning for tumor targeting. \( \text{Y}^{90} \) is the \( \beta \)-emitting isotope applied for therapeutic purposes. Chelation of \( \text{Y}^{90} \) must be of sufficiently tight binding to prevent free isotope release and to avoid marrow accumulation resulting from the relapse of free isotope. The Hybritech chelated antibody is biologically slowly degraded (8). Because the non-tumor bound chelated isotope resides in the normal liver and spleen and does not leave the body, there is potential for increased hematological toxicity due to irradiation of circulating stem cells. In the event of antibody production with the use of \( \text{Y}^{90} \), free \( \text{Y}^{90} \) would be released from the chelate (17). This possibility has necessitated a pretreatment radioimmunoassay for antibody production and a pretreatment \( \text{In}^{111} \) scan of the tumor to reassure the clinical investigator of the potential efficacy of the \( \text{Y}^{90} \)-labeled antibody infusion. \( \text{Y}^{90} \) antibody infusion should not be carried out without both pretreatment surveys, i.e., radioimmunoassay for anti-antibody and \( \text{In}^{111} \) pretreatment scan.
Knowledge of the early kinetics of antigen-antibody binding remains unknown.

Progress to Date

Our personal experience with over 2400 radioactive antibody infusions using 131I indicate that conversion of nonresectable hepatocellular cancer to resectable is possible (12), and that complete remission is achievable in selected patients (12). New drug integration is anticipated to increase the resectability rate and the complete remission rate both for AFP-deficient and AFP-containing hepatocellular cancer.

In Hodgkin's disease chemotherapy failures, 131I-antiferritin infusion achieved 40% partial remission in 37 patients (10). Data gained from these studies indicate that hematopoietic toxicity was the limiting factor (10, 27). The use of 90Y-antiferritin satisfied the dose-response requirements and has led to complete remissions in several patients receiving at least two cycles of treatment (8, 27). In addition, the issue of autologous bone marrow to avoid unacceptable hematological toxicity has been successful in these preliminary studies.

DeNardo et al. (28) have reported partial remissions with iodinated antibodies in non-Hodgkin's lymphoma. Epenotus has pioneered i.p. and intrapleural radioactive antibody therapy and gained some complete remissions (25, 26). Lashford et al. (9) have explored intrathecal therapy, and a preliminary exploration of intraarterial therapy has been carried out by Tang (29). As anti-antibody production with murine monoclonal infusions remains a limiting factor in radiolabeled antibody therapy, chimeric human murine antibodies, and chemical modifications are presently being investigated.

Toxicity

In all of the early trials reported, hematological toxicity remains prominent (30). The lack of a protective effect by lower dose rates makes this normal tissue more susceptible. The use of autologous and, perhaps later, allogeneic marrow may allow for greater doses of radiolabeled antibodies. The excretory and secretory patterns of new chelates and other isotope linkages to antibodies may well lead to organ toxicities as yet unreported.

We conclude from all of the clinical studies that the proper administration of radiolabeled antibodies does not produce undue acute effects and has been predominantly limited by hematological toxicity and the production of anti-antibodies. It is anticipated that the latter problem will be solved. At present, the number of possibilities for clinical trials exceeds their actual implementation. Carefully constructed laboratory rationales and clinical evaluations will undoubtedly progress as new data are gathered (31).

References

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