renewed interest in this methodology, which in turn will lead to more rational trial designs for immunotherapy as well as RIT.

Several key questions emerge. Among these are:

(1) How may we increase RIT awareness among referring physicians? What are the causes of RIT failure?
(2) Does dosimetry have a role in RIT development?
(3) Will RIT in solid tumors ever be feasible? Should it be pursued as single agent or only in multimodality settings?
(4) Antibody PET: Is it an intellectual curiosity or a development tool?

## REFERENCES

1. Nowakowski GS, Witzig TE. Radioimmunotherapy for B-cell non-Hodgkin lymphoma. *Clin Adv Hematol Oncol.* 2006;4:225–231.
2. Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol.* 2001;19:3918–3928.
3. Kaminski MS, Tuck M, Estes J, et al. $^{131}$I-tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med.* 2005;352:441–449.
4. Divgi CR, Scott AM, Dantis L, et al. Phase I radioimmunotherapy trial with iodine-131-CC49 in metastatic colon carcinoma. *J Nucl Med.* 1995 36:586-592.
5. Billetta R, Lobuglio AF. Chimeric antibodies. *Int Rev Immunol.* 1993;10:165–176.
6. Caligiuri MA, Velardi A, Scheinberg DA, Borrello IM. Immunotherapeutic approaches for hematologic malignancies. *Hematology Am Soc Hematol Educ Program.* 2004;337–353.
7. Divgi CR, O'Donoghue JA, Welt S, et al. Phase I clinical trial with fractionated radioimmunotherapy using $^{131}$I-labeled chimeric G250 in metastatic renal cancer. *J Nucl Med.* 2004;45:1412–1421.
8. Ratain MJ, Eckhardt SG. Phase II studies of modern drugs directed against new targets: if you are fazed, too, then resist RECIST. *J Clin Oncol.* 2004;22: 4442–4445.
9. Esteves FP, Schuster DM, Halkar RK. Gastrointestinal tract malignancies and positron emission tomography: an overview. *Semin Nucl Med.* 2006;36:169–181.
10. Gopal AK, Gooley TA, Maloney DG, et al. High-dose radioimmunotherapy versus conventional high-dose therapy and autologous hematopoietic stem cell transplantation for relapsed follicular non-Hodgkin lymphoma: a multivariable cohort analysis. *Blood.* 2003;102:2351–2357.
11. Tempero M, Leichner P, Baranowska-Kortylewicz J, et al. High-dose therapy with 90-yttrium-labeled monoclonal antibody CC49: a phase I trial. *Clin Cancer Res.* 2000;6:3095–3102.
12. Jurcic JG, Larson SM, Sgouros G, et al. Targeted alpha particle immunotherapy for myeloid leukemia. *Blood.* 2002;100:1233–1239.
13. Reardon DA, Akabani G, Coleman RE, et al. Salvage radioimmunotherapy with murine iodine-131-labeled antitenascin monoclonal antibody 81C6 for patients with recurrent primary and metastatic malignant brain tumors: phase II study results. *J Clin Oncol.* 2006;24:115–122.
14. Alvarez RD, Huh WK, Khazaeli MB, et al. A phase I study of combined modality (90)Yttrium-CC49 intraperitoneal radioimmunotherapy for ovarian cancer. *Clin Cancer Res.* 2002;8:2806-2811.
15. Forero A, Weiden PL, Vose JM, et al. Phase 1 trial of a novel anti-CD20 fusion protein in pretargeted radioimmunotherapy for B-cell non-Hodgkin lymphoma. *Blood.* 2004;104:227–236.
16. Rossi EA, Goldenberg DM, Cardillo TM, McBride WJ, Sharkey RM, Chang CH. Stably tethered multifunctional structures of defined composition made by the dock and lock method for use in cancer targeting. *Proc Natl Acad Sci USA.* 2006;103:6841–6846.
17. Divgi CR, Welt S, Kris M, et al. Phase I and imaging trial of indium 111-labeled anti-epidermal growth factor receptor monoclonal antibody 225 in patients with squamous cell lung carcinoma. *J Natl Cancer Inst.* 1991;83:97–104.
18. Daghighian F, Pentlow KS, Larson SM, et al. Development of a method to measure kinetics of radiolabelled monoclonal antibody in human tumour with applications to microdosimetry: positron emission tomography studies of iodine-124 labelled 3F8 monoclonal antibody in glioma. *Eur J Nucl Med.* 1993;20:402–409.
19. Philpott GW, Schwarz SW, Anderson CJ, et al. RadioimmunoPET: detection of colorectal carcinoma with positron-emitting copper-64-labeled monoclonal antibody. *J Nucl Med.* 1995;36:1818–1824.

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# Recent Advances in Biomarkers for Diagnosis and Treatment

Recent advances in understanding of the genetic and epigenetic abnormalities that induce development of different tumors provide the opportunity for personalized molecular medicine in cancer patients. However, the effective implementation of tumor-targeted therapeutics and fulfillment of the promise of personalized molecular medicine will require the development of approaches to identify patients likely to respond to a specific targeted drug or combination of therapeutics as well as approaches to identify patients responding and not responding at early stages of such treatments. Thus there is an urgent unmet need to develop approaches to efficiently evaluate novel targeted therapeutics and integrate them into clinical practice.

Advanced molecular–genetic and cellular multimodality imaging represents an organic fusion of radiology, nuclear medicine, and molecular and cellular biology that can provide unprecedented capabilities for noninvasive imaging of various biomarkers, including applications in: detection of precancerous lesions, early detection of tumor lesions (i.e., host tissue reaction to intraepithelial neoplasia), tumor profiling and selection of individualized therapies (visualization of drug target expression and activity), determination of biologically relevant doses (visualization and quantitation of drug target occupancy to saturation), early assessment of therapeutic efficacy (visualization of downstream processes, such as glucose metabolism, proliferation, apoptosis, etc.), monitoring the development of resistance to therapy (i.e., imaging P-glycoprotein expression/activity, estrogen or androgen receptor expression, etc.), monitoring of recurrence (i.e., differentiation of radiation necrosis from recurrence), and long-term prognosis.

Several novel and previously developed molecular imaging agents and methods (i.e., FDG, fluorothymidine,

methionine, annexinV, perfusion/permeability imaging, etc.) can facilitate the development and clinical translation of novel tumor-targeted molecular therapies. For particular targeted therapies, molecular imaging agents should be developed for visualization and quantitation of the level of target expression and activity or "expression/activity product" (i.e., level of HER2/neu or epidermal growth factor receptor expression and activity). In contrast to invasive single- or multiple-site biopsies, noninvasive whole-body molecular imaging will allow for the assessment of spatial and temporal heterogeneity of target protein expression/activity in tumors, monitoring the activity of relevant downstream signaling events, and for imaging more general processes in tumors (metabolism, proliferation, apoptosis, etc.) during therapy. In phase 0/I clinical trials of novel molecular-targeted drugs, molecular imaging can provide the means for noninvasive assessment of pharmacokinetics of a new drug using radiolabeled versions of this drug, as well as pharmacodynamic assessment of pharmacological microdosing by noninvasive repetitive imaging of changes in the activity of downstream effectors and/or processes in tumor tissue and in the whole body.

Furthermore, noninvasive molecular imaging of spatial heterogeneity of target expression and activity should facilitate image-guided therapeutic interventions (i.e., radiation therapy), as well as image-guided biopsies in areas with high and low target expression/activity. The latter should significantly improve the statistical significance and reproducibility of genomic and proteomic analyses and will allow for identification of more reliable biomarkers. Integration of molecular imaging biomarkers and image-guided biopsies into clinical trials and clinical management will allow 1) the selection of patients likely to respond to specific targeted therapies (to enrich the patient population that is likely to respond); 2) monitoring the biological efficacy of a given targeted therapeutic, allowing dose alteration and optimization at an early stage of therapy; and 3) facilitating triage to the most appropriate therapy, thereby containing patient costs.

Using multitracer and multimodality imaging approaches, it will be possible to develop differential-diagnostic algorithms that can be used routinely by analogy with invasive histopathological and molecular biological biomarker methods for profiling of individual cancers and for selection (and monitoring) of individualized combination therapies. The latter represents a major shift in product development strategy for industry—from aiming to develop the next "killer application" imaging agent toward the development of a disease-oriented portfolio of imaging agents that may be shared between different tumor types and may even be used for diagnosis, profiling, and therapy monitoring of other nononcological diseases.

In summary, tissue biomarkers and corresponding targeted agents for noninvasive imaging should be developed in parallel with novel targeted therapeutics. These biomarkers and imaging agents should allow for identification of patients who are likely to respond to targeted therapeutics and for triage to the most appropriate therapy. The latter has the potential to greatly improve patient outcomes and decrease toxicity. Integration of molecular markers and molecular imaging into clinical trials and clinical management will allow for: the selection of patients likely to respond to specific therapies, determination/optimization of biologically effective (not maximum tolerated) doses, assessment of responses to the selected therapies at an early stage of treatment to allow for triage to the most appropriate therapy, and improvement in overall outcomes.

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