

# Adjuvant and Combined Radioimmunotherapy: Problems and Prospects on the Road to Minerva\*

One of the results of reviewing a provocative article is that the Editor-in-Chief sometimes provides the opportunity, or maybe the challenge, to comment. I choose to relate my thoughts on this article to Minerva, because of her being the goddess of medical and other technical applications, which I think is the importance of the article by Koppe et al. (1) in this

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issue of *The Journal of Nuclear Medicine*. It demonstrates the success of applying radioimmunotherapy (RAIT) in an opportune and important disease setting for colorectal and other intraabdominal cancers. As we have come to realize, RAIT is more successful in hematopoietic than in solid tumors (2–5). So what are its prospects in solid tumor therapy, where existing treatment options are, in most cases, of

limited value, and where efficacy may be improved by combining it with therapeutic modalities that by themselves are less active? This article points to an option for RAIT in combination with surgery for improving the management of cancer that has local seeding, particularly in an accessible cavity. This is consistent with the potential use of RAIT as an adjuvant therapy for micrometastatic or minimal residual disease (6,7) or after salvage resection of liver metastases from colorectal cancer (8).

weight. (iv) The more direct the therapy, the higher the anticipated dose delivered to the tumor. (v) Different clinical settings (tumor type, stage, burden, host status in terms of prior therapy, concomitant conditions, and so forth) can give different results even with the same agent. (vi) Most phase I and phase II clinical trials strive to determine safety and any evidence of efficacy in patients with advanced disease, who have failed other therapies, who have bulky disease, and who may not even survive until the minimal duration of evaluation is reached. The results of these early-stage trials usually discourage further studies in better settings. Yet, from a clinical perspective, there is evidence that the 2 approved RAIT products are superior to their naked antibody counterparts (9,10) and are now, appropriately, gaining adoption in earlier therapy regimens (11,12).

External beam radiation works best when there is localized disease and when the dose is fractionated. Conversely, I believe that RAIT works best when there is low-burden, disseminated disease and probably also when it is fractionated (13). Indeed, laboratory and human studies show that the best effects are in settings of minimal or occult disease (6–8,14,15), and evidence is also emerging that RAIT can be combined effectively with chemotherapy in solid tumors (16–18). In this article (1), RAIT has been shown to improve the efficacy of surgery.

This study by Koppe et al. (1) is the latest of a series that has stepwise and logically considered the route of administration (19) and the radionuclide (20) when treating tumor seeding of the peritoneal cavity, or carcinoma-tosis. Prior studies with anticarcinoma-embryonic antigen antibodies in



Head of Minerva by Elihu Vedder, 1896 (from Wikipedia).

Let me begin with some generalizations. (i) Any tumor will respond if given enough radiation. (ii) Right now, such doses are not achievable because of host toxicities, except in hematopoietic tumors, where improved vascularization may play a role. (iii) The smaller the tumor, the higher the radiation dose delivered per size or

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\*According to the encyclopedia Wikipedia, Minerva was the daughter of Jupiter and Metis and the virgin goddess of medicine, wisdom, and crafts, among other attributes, such as the inventor of music. But she is especially noted for practical applications of engineering and technology and, as *Minerva Medica*, was the goddess of medicine and doctors. In *Plutarch's Lives: Pericles*, Pericles dreams of Minerva prescribing treatment for an injured citizen of Athens, who was cured, and this resulted in a brass statue being erected in her honor. In more contemporary times, Minerva is the logo of the German Max Planck Society (Max-Planck-Gesellschaft), she is featured on the seal of California, is one of the concluding sections of each issue of the *British Medical Journal*, and is featured on the seals and logos of the State University of New York at Albany, the University of Alabama, and Union College.

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a carcinomatosis model of human colorectal cancer showed the advantages of the intraperitoneal route and the use of  $^{131}\text{I}$  or  $^{177}\text{Lu}$  for short-range irradiation when small lesions are involved (19,20). The studies now reported test this in a syngeneic rat tumor model that evaluated intraperitoneal RAIT alone, cytoreductive surgery alone, and their combination, with evidence of statistically improved survival for the combination. Because intraperitoneal spread is a challenging clinical problem occurring in 10%–47% of patients undergoing colorectal cancer surgery (1,21) and has been managed with intraperitoneal chemotherapy (22), intraperitoneal RAIT is quite logical to pursue. However, the experience of intraperitoneal RAIT in patients with ovarian cancer, which also deals with peritoneal spread, needs to be considered before clinical trials in colorectal cancer are undertaken, as it is likely that many of the conditions will be the same. In ovarian tumors and in other tumors in an intracavitary setting, the intraperitoneal route has been found to be preferred for administering RAIT (23–25), various radionuclides have been shown to be effective, with few direct comparisons being made (26), and a large randomized trial comparing intraperitoneal RAIT with the standard of care in ovarian cancer failed to show a survival difference (27)—thus, raising concern as to the clinical prospects of intraperitoneal RAIT in colorectal carcinomatosis.

The negative results of the randomized trial of RAIT in patients with occult ovarian cancer, based on laparoscopy (27)—though disappointing—raise questions retrospectively with regard to trial design, such as use of a murine antibody, giving only 1 injection of RAIT, using  $^{90}\text{Y}$  as a deep-penetrating emitter in occult disease, and permitting investigator-defined consolidation chemotherapy after RAIT or standard care, to mention a few. My own inclination is to administer fractionated doses, to consider combining intraperitoneal with intravenous administration, and to standardize

consolidation or even combining chemotherapy among the treatment arms. Indeed, there is evidence that, whereas the intraperitoneal route may be more efficacious than intravenous RAIT, there is a rationale for combining both to reach pockets of cancer cells that are not targeted by intracavitary application (28). Finally, in terms of choice of radionuclide, selection is usually made from what is available and not what would be best, and, in this regard, occult or micrometastatic disease should be more responsive to radionuclides with shorter pathlengths and higher energies, such as  $\alpha$ -emitters (29,30).

Finally, methods are now being developed to achieve more selective targeting of radionuclides to tumors by pretargeting, where tumor localization by antibody is separated contemporaneously from the subsequent administration of the therapeutic (31). The markedly increased ratios of tumor to nontumor, including to blood and bone marrow, and the higher uptake in tumor achieved as compared with direct RAIT, all suggest that, particularly in an intracavitary setting, pretargeted RAIT may be advantageous, allowing higher tumor doses without commensurate myelosuppression (32,33). Indeed, intraperitoneal pretargeted RAIT has demonstrated encouraging therapeutic results in an experimental model (34). Also, combining pretargeted RAIT with chemotherapy in resected gliomas is showing improved outcome (35). Thus, the road to Minerva is becoming passable, and solid tumor RAIT, at least in certain defined settings, may yet gain a role in cancer treatment.

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