Editorial

Treating Hodgkin’s Disease with Bispecific Antibodies: Both Patients and Antibody Are Limiting

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The clinical trial reported by Hartmann et al. later in this issue of Clinical Cancer Research represents a triumph of clinical research conducted in a rare patient population with a limited quantity of a therapeutic reagent. Despite the fact that Hodgkin’s disease is an uncommon cancer, i.e., only 7100 cases were diagnosed in the United States in 1998, it has been a model for therapeutic advances beginning with curative radiotherapy and combination chemotherapy (1). Today the number of patients with Hodgkin’s disease who are available for clinical trials of new treatment modalities is additionally reduced by the fact that >75% of all patients with Hodgkin’s disease are cured by standard treatments. All of the patients who might enter Phase I/II clinical trials have been extensively pretreated and have a disease that has been refractory to combination chemotherapy with or without radiotherapy; most younger patients have also undergone autologous stem cell transplantation. New studies have continued in Germany where >75% of all patients with Hodgkin’s disease enter clinical trials; this has become increasing difficult in the United States where only 3–5% of all patients enter clinical research protocols.

Research and development into the treatment of patients with bispecific antibodies has been significantly slowed and limited by problems of manufacturing. This remains true in the studies with this anti-CD16/CD30 bispecific monoclonal antibody. The initial Phase I/II trial from the same group demonstrated that the antibody was well tolerated and induced 2/15 objective antitumor responses; unfortunately, the maximally tolerated dose could not be defined because of limited drug supply (2). In the current study, 4 of 16 patients (25%) had objective antitumor responses (one complete remission and three partial remissions) that lasted from 5 to 9 months. Although this is quite encouraging for a heavily pretreated patient population, this study leaves unresolved many other issues. This limited number of patients was treated with two different administration schedules, either continuous infusion for 4 days or 1-h infusions every other day. Because three of the four responses occurred after continuous infusion, it is tempting to consider that schedule optimal although the small numbers of patients make that conclusion far from certain. In addition, patients with stable disease after one cycle of treatment with the bispecific antibody alone were retreated with IL-22 pretreatment followed by bispecific antibody and then granulocyte macrophage colony-stimulating factor. Again it is tempting to conclude that this additional therapy was useful because two of the four responding patients (one complete and one partial remission) each received the combined treatment; however, additional study is needed.

The suggestion that treatment by continuous infusion of the antibody in conjunction with both IL-2 and granulocyte macrophage colony-stimulating factor was optimal can be supported by data derived from measurements of immune function in the peripheral blood of the patients. However, Hodgkin’s disease may be one of examples where the so-called “optimal biological dose” may not be defined by measurements in the peripheral blood. The biology of Hodgkin’s disease is unique. It is a disease of the lymphatic organs and not, in general, the blood. When lymph nodes from patients with Hodgkin’s disease are examined, the malignant cells, i.e., the Reed-Sternberg cells, are rare. The bulk of the nodal infiltrate is an inflammatory infiltrate comprised of lymphocytes, monocytes, granulocytes, eosinophils, and others. The Reed-Sternberg cell has in fact been demonstrated to produce multiple cytokines including IL-1, -5, -6, -7, -9, and -10, and so on (3). It also expresses multiple cytokine receptors. Thus, the lymph node involved in Hodgkin’s disease is obviously a site of extraordinarily complex immune interactions; it is likely that monitoring immune reactivity in those lymph nodes, although clinically difficult, will be critical to understanding the biological mechanisms that result in the antitumor activity of these antibodies.

This report adds important information to the ongoing debate about the biological impact of HAMA formation. Does HAMA formation limit retreatment with the same antibody? Will HAMA limit retreatment with different antibodies? The answers to these questions may also be disease specific, i.e., the incidence of HAMA formation appears higher in patients with solid tumors than that observed with patients with lymphoma where the underlying immune deficit may limit the incidence and magnitude of HAMA formation. On the basis of data presented in this paper, the answers may also be dependent on the manner in which the antibody is infused. The majority of patients in the initial Phase I/II trial of this bispecific antibody developed HAMA, and allergic reactions prevented subsequent retreatment with the same antibody in all of the five cases in which it was attempted. In that study the antibody was administered for 1 h. In the current study, a relatively weak HAMA response was observed in six patients (37.5%). Three of those patients were retreated without any adverse reactions. More research in this area is clearly indicated.

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2 The abbreviations used are: IL, interleukin; HAMA, human antimouse antibody; NK, natural killer.
Finally, one must wonder if the clinical success demonstrated in patients with Hodgkin’s disease in this article relates specifically to use of the anti-CD16 targeting of NK cells by this bispecific antibody. Recall that patients with Hodgkin’s disease, both at diagnosis and also after therapy, have underlying immunodeficiency especially of cellular immunity (4). Thus, attempts at immunotherapy that require T-cell recognition and effector function may be difficult. In contrast, NK cell function in patients with Hodgkin’s disease is generally preserved. The current clinical trial is certainly promising enough to justify future studies aimed at directing NK cells to the Reed-Sternberg cell. However, there is no immediate hope of generating unlimited amounts of this bispecific antibody. We look forward to future studies of this group with chimeric or completely humanized bispecific F(ab’)2 fragments.

References
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