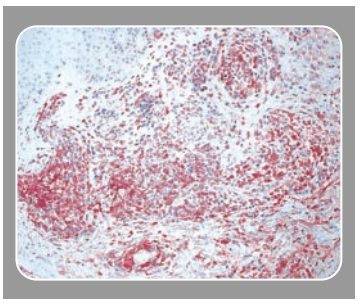
inside blood

Tackling T-cell tumors

Cutaneous T-cell lymphomas represent a tumor with a defined target, the somatically rearranged T-cell receptor (TCR), that should represent a tumor-specific immunologic target analogous to the idiotype (Id)–specific target of B-cell lymphomas. The Id antigen on B-cell lymphomas has been targeted by Levy and others using a variety of vaccine approaches and large prospective clinical trials of this strategy are ongoing. The secreted antibody associated with myeloma has also been demonstrated to be processed and presented on malignant B cells and could be recognized by antigen-specific T cells.[1] Although much less common than B-cell malignancies, the TCR



on T-cell malignancies also represents an attractive immunotherapy target. Unfortunately, the TCR is not secreted and capturing the antigen from an individual's tumor for the creation of a vaccine usually involves creating a whole tumor lysate.

Maier and colleagues (page 2338) performed this experiment, vaccinating 10 cutaneous T-cell lymphoma patients with tumor lysate pulsed onto autologous dendritic cells (DCs) loaded with tumor lysate and given by intranodal injection.[2] Intranodal injection appears to be a important route of delivery since the initial observation that intravenous and subcutaneous delivery in humans lead to little trafficking to lymph nodes, whereas only a fraction of DCs injected into the dermis trafficked to draining lymph nodes.[3]

In this report, Maier and colleagues have shown the induction of antigen-specific T-cell responses and clinical response in patients with cutaneous T-cell lymphoma. The authors noted that delayed-type hypersensitivity to the tumor lysate was increased in treated patients and recognition of autologous tumor cells by peripheral blood mononuclear cells (PBMCs) following vaccination compared with PBMCs obtained prior to vaccination as determined by cell proliferation and cytokine release assays. Significant recognition was notable in 3 patients, all of whom had a clinical response (1 complete and 2 partial responses). One element that was not specifically addressed by this study was whether an immune response to the specific TCR of each tumor was induced.

Nonetheless, the potential to target malignant T-cell tumors is demonstrated in this pilot study. The feasibility and utility of DC vaccination by the intranodal route is again highlighted. Finally, the correlation of autologous tumor-specific immune responses with clinical responses is provocative. The authors did not demonstrate specific immune responses against the TCR of each tumor, a finding that would have important indications for the treatment of this malignancy but also for the therapeutic elimination of T-cell clones in autoimmune disorders. Further investigation of immunotherapy in this promising model system is certainly warranted.

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2. Nestle FO, Alijagic S, Gilliet M, et al. Vaccination of melanoma patients with peptide- or tumor lysate-pulsed dendritic cells. Nat Med. 1998;4:328-332.
3. Morse MA, Coleman RE, Akabani G, Niehaus N, Coleman D, Lyerly HK. Migration of human dendritic cells after injection in patients with metastatic malignancies. Cancer Res. 1999;59:56-58.

To each according to his need

It is the aim of medical science to increase our capacity to treat effectively the most severe manifestations of disease. It is our expectation that society will reward this pursuit of new medical knowledge by providing the enabling resources to translate it to better care for patients. The report in this issue of *Blood* by Gringeri and colleagues (page 2358) entitled "Cost of care and quality of life in hemophilia complicated by inhibitors: the COCIS Study Group" provides compelling data that extensive investment in this particularly problematic subset of the hemophilia population, when applied in the context of a comprehensive hemophilia treatment center care model, can result in an acceptable quality of life for most of these individuals. Certainly the costs for such care, when individualized, are extraordinary: approximately €18 000 per month. This is a cost that is consistent with earlier reports[1] and reflects overwhelmingly the expense associated with the need to use "by-passing" coagulation factor concentrates to achieve hemostasis. As the authors indicate, a significant portion of these exceedingly high costs is attributable to the need for these bypassing agents, and to provide hemostasis for restorative surgery and the resultant rehabilitation—all legacies of the high morbidity of a long-standing factor VIII or IX inhibitor.

Two significant observations distinguish this publication. First, since the cohort is drawn from approximately one third of the individuals meeting accepted definitions of inhibitor classification in a large country (Italy), it permits the authors to extrapolate the cost of care for these rare individuals across the society's entire health care delivery system—an estimated 0.70 per Italian citizen per year. This enables the disinterested observer to place the costs in context. Second, the employment of validated

quality-of-life methodology to the scrupulously collected cost data allows determination of an expenditure for expected clinical impact to be determined. Again this provides a contextual framework for comparing this significant morbidity to other required clinical interventions by the health care system. For extreme cost outliers, like hemophilia with inhibitors, this is necessary both to justify the expenditures and to define strategies to increase positive clinical impact per monetary unit expended. Further, it may well justify expanded research into more aggressive and costly strategies for morbidity *prevention* in the hope that the up-front costs will ultimately diminish costly rehabilitative services later.

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The title is ascribed to Karl Marx 1875 from Critique of the Gotha Program; it was in quotes by Marx and may have originated with Louis Blanc (1811-1882) or Morelly (1840).

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The evolution of hematopoietic stem cell transplantation for multiple sclerosis

Multiple sclerosis, commonly referred to as MS, is a disease that hematologists do not commonly encounter in their clinical practices. However, MS is the most common demyelinating disease and is characterized by focal destruction of myelin sheaths in the central nervous system accompanied by an inflammatory response. Clinically, MS may persist for more than 30 years with neurologic symptoms, which occur, remit, and recur. Symptoms of MS can be extremely debilitating and include impaired vision, decreased perception and position sense, ataxia, bladder dysfunction, muscle weakness, and paralysis. The exact cause of MS is unknown but current opinion is that it is an autoimmune disease, which is perhaps induced by a viral illness or environmental factors in genetically susceptible individuals. Typical treatments include several immune-based therapies such as corticosteroids, beta-interferons, cyclosporine, plasma exchange, azathioprine, and cyclophosphamide.

Similar to their application in hematologic malignancies, the dose-limiting toxicity of many immunosuppressive agents, such as cyclophosphamide, is hematologic. As such, there was significant clinical interest as to whether the administration of high doses of these agents with hematopoietic support would result in stabilization or improvement in MS and other autoimmune diseases such as rheumatoid arthritis. The first publications on autoimmune diseases treated with high-dose immunosuppressive agents with hematopoietic stem cell transplantation appeared only in late 1996. The number of patients with autoimmune diseases that received transplants has expanded rapidly such that more than 400 treated patients have been described and reported to the European League Against Rheumatism/European Group for Blood and Marrow Transplantation database. The largest number of these patients has the diagnosis of MS.

In this issue of *Blood*, 2 studies highlight the significant progress that has been made in the investigation of hematopoietic stem cell transplantation as treatment for MS. These 2 studies demonstrate that this treatment has evolved beyond anecdotal novelty to address several important issues such as unique toxicities with transplantation and, more importantly, the evaluation of which patients are most appropriate to be considered for this treatment. Nash and colleagues (page 2364) describe the results of a multi-institutional pilot study in which 26 patients with advanced MS received high-dose cyclophosphamide, total body irradiation, and antithymocyte globulin followed by CD34-selected autologous stem cell transplantation. This study points out that there are several complications with transplantation that are relatively unique to MS. These included flairs of disease with cytokine mobilization and relatively high incidences of bladder complications and engraftment syndrome. Burt and colleagues (page 2373) observed similar complications in their single-institution trial, which included 21 MS patients and used a similar immunosuppressive regimen with higher doses of radiation and omission of antithymocyte globulin. An important observation from this latter trial was the lack of efficacy in MS patients with more advanced neurologic progression, as defined by the expanded disability status scale (EDSS). Specifically, there was minimal to no evidence of disease stability in patients with EDSS scores greater than 6.0. The authors hypothesized that intensive immunosuppression may be of little or no benefit in patients late in their disease course, which is characterized more by axonal degeneration than by an active inflammatory process.

Both of these studies highlight the complexity of treating MS and the absolute necessity for a multidisciplinary approach for proper protocol execution. Their design, observations, and data interpretation provide both a detailed template and suggest appropriate research questions for future trials. These studies also suggest that hematopoietic stem cell transplantation has further evolved from a method to replace defective stem cells and administer high-dose cytotoxic therapy for cancer to an immunotherapeutic approach for nonmalignant diseases. As the number of patients with autoimmune disease far exceeds the number of patients with malignancy, it is not inconceivable that in the future the most common indication for hematopoietic stem cell transplantation will be for autoimmune diseases. As such, hematologists involved with transplantation are going to have to refamiliarize themselves with diseases that they have not had to particularly think about since medical school or residency. Similarly, several specialties may have to develop expertise in hematopoietic stem cell transplantation or possibly an entirely new specialty of hemato-immunotherapy will emerge.

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