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Graft-versus-host disease (GVHD) remains the major problem to be overcome in allogeneic bone marrow transplantation [1–3]. Despite posttransplant immunosuppressive therapy with cyclosporine or methotrexate, moderate to severe acute GVHD develops in approximately 45% of transplant recipients with an HLA-identical sibling donor [4] and in >75% of patients from HLA-nonidentical relatives [5]. Recently, bone marrow transplants have been performed from unrelated HLA-identical or partially matched related donors [6–10]. Preliminary results indicate that even with phenotypically identical unrelated donor-recipient pairs and the use of combination posttransplant immunosuppressive therapy, the incidence of acute GVHD exceeds 75%.

The pathophysiology of graft-versus-host disease is complex and incompletely described. Data in animals and humans indicate that it is largely mediated by immunocompetent T-cells in the donor bone marrow graft that are reactive against recipient (host) tissues [1,2]. In mice, depletion of T lymphocytes from the donor bone marrow by treatment with anti-Thy-1 antibody and complement effectively prevents GVHD in major histocompatibility complex (MHC) compatible and incompatible transplants [11–15]. T-cell depletion is also effective to prevent graft-versus-host disease and its associated mortality in rats, dogs, swine, and monkeys transplanted across major or minor histocompatibility barriers [15]. Failure of engraftment is a more frequent problem following T-cell-depleted transplants, particularly with MHC nonidentical donor-recipient pairs; this can be overcome in murine models by using high cell doses and more intensive pretransplant conditioning [16].

T-cell depletion in humans

Methods of T-cell depletion

T-cell depletion has been extensively studied in man, primarily in patients receiving bone marrow transplantation for leukemia [17–19]. A number of techniques have been utilized. Most studies have used ex-vivo treatment of
the donor bone marrow with single or multiple monoclonal anti-T-cell antibodies. The most commonly used monoclonals are the broadly reactive human Campath-1 antibody [20] or pan-T-cell reactive agents such as anti-CD3 [21,22] or anti-CD2 [23].

Initial studies involved incubation of the marrow with antibodies alone and infusion of the treated cells into the transplant recipient [21,22]. This approach assumes that the antibody-coated cells will be eliminated by effector mechanisms in the recipient that are likely to be defective following high-dose cytotoxic therapy. These studies were unsuccessful in substantially reducing the incidence and severity of graft-versus-host disease. Most subsequent studies have involved ex-vivo treatment with monoclonal antibodies and complement [20,23-29]. The use of complement has several limitations. Most murine monoclonals fix complement poorly. The source of complement has generally been rabbit serum; individual lots must be carefully screened since they vary considerably in effectiveness and may have nonspecific toxicity. There is considerable interest in developing alternative T-cell depletion methodologies, such as using antibodies bound to ricin or other toxins (immunotoxins) [30] or using anti-T-cell antibodies conjugated to iron beads with physical removal of the antibody-bound target cells by a magnetic field [31]. Other commonly used methods include soybean lectin agglutination and E-rosette formation [32] or counterflow elutriation [33]. The efficacy of T-cell depletion must be monitored, ideally using limiting dilution analysis [34,35]; these techniques generally achieve a 1.5–4 log (95–99.99%) reduction of T-cells.

**Clinical results**

**Graft-versus-host disease**

T-cell depletion has been uniformly successful in reducing the incidence and severity of acute GVHD. For recipients of T-cell-depleted transplants from HLA-identical sibling donors, the incidence of acute GVHD is reduced to 5–20%, primarily restricted to mild to moderate cutaneous involvement. With effective depletion (generally ≥three logs of T-cells), posttransplant immune suppression is unnecessary for prevention of acute graft-versus-host disease, although a recent analysis by the International Bone Marrow Transplant Registry noted that the rate of acute GVHD was further reduced in patients receiving posttransplant cyclosporine and/or methotrexate [17]. Mortality related to acute GVHD is largely eliminated [23,29]. The incidence of chronic graft-versus-host disease is also reduced [17,23]. Following unmodified transplants from HLA-nonidentical donors, graft-versus-host disease occurs in ≥75% of recipients of unmodified bone marrow and is a major cause of morbidity and mortality; with T-cell-depleted transplants, <30% develop moderate to severe GVHD [18]. This approach has allowed successful transplants from haploidentical donors for patients with severe