Mesenchymal stem cells targeting the GVHD

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Acute graft-versus-host disease (GVHD) occurs after allogeneic hematopoietic stem cell transplant and is a reaction of donor immune cells against host tissues. About 35%—50% of hematopoietic stem cell transplant (HSCT) recipients will develop acute GVHD. It is associated with considerable morbidity and mortality, particularly in patients who do not respond to primary therapy, which usually consists of glucocorticoids(steroids). Most of the available second-line and third-line treatments for steroid-refractory acute GVHD induce severe immunodeficiency, which is commonly accompanied by lethal infectious complications. Mesenchymal stem cells (MSCs) have been shown to mediate immunosuppressive potential of mesenchymal stem cells has set the stage for their clinical testing as cellular immunosuppressants, MSCs have been used in patients with steroid-refractory acute GVHD, and encouraging responses have been obtained in many studies. The utility of MSCs for the treatment of GVHD is becoming clear.

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Graft-versus-host disease (GVHD) is the most frequent complication after allogeneic bone marrow or hematopoietic stem cell transplantation (HSCT). First described as “secondary disease” in mice[1], the syndrome was shown to be triggered by immunocompetent donor cells[2−3].

Although the prognosis of acute GvHD (aGvHD) has dramatically improved in the last few years, morbidity and mortality from aGvHD remain the main cause of unsuccessful allogeneic HSCT. Approaches to therapy of acute refractory GVHD to “standard” doses of steroids have ranged from increasing the dose of steroids to the addition of polyclonal or monoclonal antibodies, the use of immunotoxins, additional immunosuppressive/chemotherapeutic interventions, phototherapy, and other means. Although many pilot studies have yielded encouraging response rates, the long-term survival was not improved in comparison with that seen with the use of steroids alone[4].

Mesenchymal stem cells are multipotent adult stem cells capable of generating osteoblasts, myoblasts, chondroblasts, adipocytes and stromal cells[5]. MSCs have recently been shown to mediate immunomodulatory properties in vitro, interacting with cellular components of the immune system and inducing a shift from pro- to anti-inflammatory cytokines[6]. By inhibiting T-cell proliferation after stimulation by alloantigens and mitogens and by preventing the activity of cytotoxic T cells, MSCs may become a useful tool in steroid-refractory aGVHD[7].

In clinical situations, these immunological features of MSCs are advantageous in GVHD following allogeneic BMT or HSCT. A potential beneficial effect of co-transplanting ex-vivo expanded MSCs together with hematopoietic stem cells (HSC) could be inferred from adult patients who developed aGvHD and cGvHD less frequently compared to historical controls when transplanted with MSC in association with allogeneic BMT[8].

1 Pathophysiology of GVHD

The pathophysiology of acute GVHD has been de-
scribed by Ferrara and colleagues as a three-phase phenomenon\(^9\) (Figure 1). The first involves damage to host tissues by inflammation from the preparative chemo- and/or radio-therapy regimen. For example, bacterial endotoxins may translocate from the intestinal lumen into the circulation and induce the release of inflammatory cytokines, including IL-1, TNF-α, IL-6 and IFN-γ\(^10\).

In the second phase, both recipient and donor antigen-presenting cells (APCs) as well as inflammatory cytokines triggering the activation of donor-derived T cells expand and differentiate into effector cells\(^9\). T-cell activation pathways result in the transcription of genes for cytokines, such as IL-2 and interferon.

In the third phase, the effector phase, activated donor T cells mediate cytotoxicity against target host cells through Fas-Fas ligand interactions, perforin-granzyme B, and the additional production of cytokines, such as TNF-α. This allogeneic interaction in the setting of cytokine dysregulation leads to the tissue damage characteristic of acute GVHD\(^11\).

2 Treatment of GVHD

2.1 First-line treatment

Steroids associated with CsA or tacrolimus are usually considered standard therapy for the first-line treatment of aGVHD. Different types and dosages of steroids are used in the initial management of aGVHD, but methylprednisolone (6MPD) given at a dosage of 2 mg/kg·d\(^{-1}\) is more frequently administered\(^12\). The efficacy of steroids in curing aGVHD, in improving the outcome and in increasing the probability of survival is acknowledged. Moreover, several side effects, such as hyperglycaemia, osteoporosis and growth defects, represent the main limitations to long-term use.

Blazar\(^13\) concluded that steroids were inadequate in severe forms of aGVHD and that more effective prophylaxis is needed for non-identical transplants or alternative donors. The Group for Marrow Transplantation has carried out prospective studies to identify the best strategy for the treatment of aGVHD\(^14\)\(-16\). The conclusions of these studies are the following: more aggressive first-line therapy is not beneficial. In particular, there were no differences in terms of transplantation related mortality (TRM) between high doses (10 mg/kg·d\(^{-1}\)) versus low doses (2 mg/kg·d\(^{-1}\)) of 6MPD, or between patients treated with ATG versus patients who received average doses (5 mg/kg·d\(^{-1}\)) of 6MPD.

Moreover, the Group for Marrow Transplantation study showed that high dose 6MPD did not prevent the

\[\text{Figure 1} \quad \text{The three phases of acute GVHD: afferent phase, induction and expansion phase and effector phase, as described by Ferrara and colleagues}^{9}.\]