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A New Approach to Therapy for Acute GVHD

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Abstract

Graft-versus-host disease (GVHD) is a principal cause of morbidity following allogeneic hematopoietic cell transplantation (HCT). Multiple pre-clinical studies have shown that tumor necrosis factor-α (TNFα) is an important effector of experimental GVHD. Patients treated with etanercept and steroids were more likely to achieve complete response than were patients treated with steroids alone. This difference was observed in HCT recipients of both related donors and unrelated donors. Cytokine blockade may become an important element of treatment for GVHD in the future.

Keywords: bone marrow transplantation, graft versus host disease, GVHD, inflammatory cytokines, TNF-alpha, steroids

Introduction

Allogeneic HCT is a curative treatment for a number of hematologic malignancies and genetic disorders. Despite the routine use of immunosuppressive agents that target T cells, such as calcineurin inhibitors, up to 50% of HCT recipients still experience significant graft-versus-host disease (GVHD) that requires treatment with high dose systemic steroids. The risk of mortality in patients who do not respond completely to initial therapy is very high, but complete response (CR) rates have remained at approximately 35%.

Animal models have established that the pathophysiology of GVHD can be conceived as a process with three phases, involving complex immunologic interactions between cellular effectors and soluble effectors, such as inflammatory cytokines (See Figure 1).

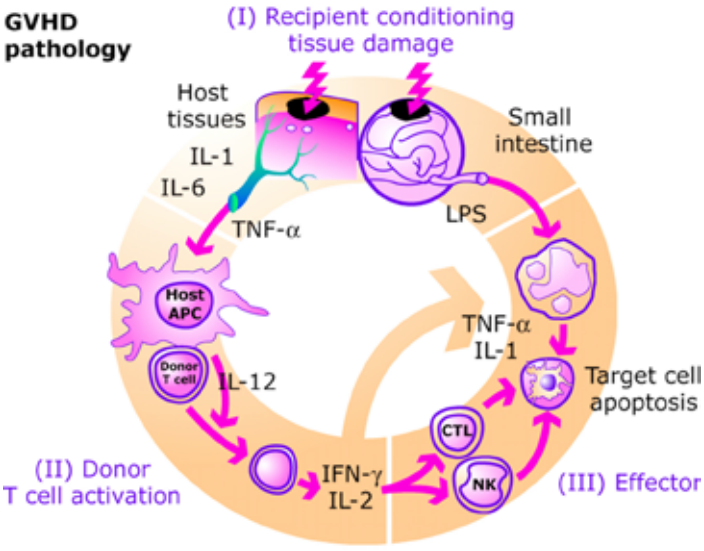

Figure 1: Phases of GVHD Pathophysiology. The development of acute GVHD can be conceptualized in three sequential steps or phases: (1) activation of the antigen presenting cells (APCs); (2) donor T cell activation, proliferation, differentiation and migration; and (3) target tissue destruction. During phase 1, the release of inflammatory cytokines such as IL-1, IL-6, and especially, TNF-α, lead to increased expression of MHC antigens and adhesion molecules, which enhance host antigen presenting cells (APCs) to present allo-antigen to donor T cells. In phase 2, mature T cells from the donor, infused into an environment primed for immunologic activation, interact with host APCs, proliferate and differentiate into activated T cells, which release additional inflammatory cytokines. In phase 3, target organ damage results from the migration of cytotoxic T lymphocytes (CTLs) and natural killer cells into the tissues. In addition, monocytes, stimulated by lipopolysaccharide (LPS) translocated across damaged intestinal mucosa, secrete cytopathic amounts of inflammatory cytokines such as TNF-α, culminating in clinically evident GVHD.

One of the most important inflammatory cytokines in GVHD pathophysiology is tumor necrosis factor-alpha (TNFα), which mediates GVHD both through the amplification of donor immune response to host tissues as well as direct toxicity to target organs. These preclinical data served as the rationale to use anti-TNFα agents. Infliximab, a monoclonal antibody directed at TNFα, binds to both soluble and membrane-bound TNFα, resulting in clearance of both circulating TNFα and T cells. Etanercept, a soluble dimeric TNFα Receptor 2, competes for TNFα binding and renders it inactive. This mechanism of action combined with its relative ease of administration by subcutaneous injection and generally minor side effects, make etanercept attractive as primary GVHD therapy.

Results

We have recently published the results of our using etanercept in addition to high dose steroids as primary therapy for acute GVHD[16].

The primary endpoint of the clinical trial was CR (resolution of all GVHD manifestations) at four weeks after the initiation of treatment. Patients treated with etanercept plus steroids were significantly more likely to achieve CR four weeks later than were patients treated with steroids alone [69% vs 33%, p<0.0001]. The benefit of etanercept persisted so that by 12 weeks after initiation of GVHD treatment, 77% of etanercept plus steroids patients had achieved CR compared to 50% of steroids alone patients (p=0.0009). We performed a univariate analysis comparing CR rates according to conditioning regimen (myeloablative vs reduced intensity), a factor known to influence GVHD[17]. A conditioning regimen did not impact CR rates in patients treated with etanercept plus steroids. In multivariate analyses the only two variables associated with increased likelihood of CR were the use of etanercept and a related donor stem cell source. Patient age, conditioning regimen, degree of HLA-match, and the day of onset of GVHD all had no statistically significant association with response.

The higher response rate seen in patients treated with etanercept plus steroids translated into improved survival at 100 days from initiation of GVHD treatment [etanercept plus steroids, 82% vs steroids alone, 66%, p=0.04]. At 6 months from initiation of treatment a higher proportion of patients treated with etanercept plus steroids were still alive (69%), compared to 55% of patients treated with steroids alone, but this difference did not meet the criteria for statistical significance [p=0.08].

Because of the trend towards an increased proportion of unrelated donor transplants in the group treated with steroids alone, we analyzed the results by stem cell source. The superiority of etanercept was evident in transplant recipients from both related donors [79% vs 39%, p=0.001] and unrelated donors [53% vs 26%, p=0.0005]. This latter difference is particularly noteworthy, because studies have shown that acute GVHD in recipients of unrelated donor transplants is more difficult to treat than GVHD in recipients of related donor transplants. The time to CR was significantly faster in recipients of related donor transplants who were treated with etanercept plus steroids, but by 12 weeks nearly equivalent proportions of patients in both groups achieved a CR (etanercept plus steroids, 80%, steroids alone 70%). It is therefore not surprising that survival six months from initiation of GVHD treatment was similar in both treatment groups. Recipients of unrelated donor transplants who failed to achieve a CR by day 28 were likely to never achieve CR, thus translating into a survival advantage six months later. Importantly, the infection rates in the first 100 days from initiation of GVHD treatment were not different between patients treated with etanercept plus steroids or treated with steroids alone for bacterial, invasive fungal or viral infections. There were no mycobacterial infections observed in any patients.

Discussion

Current standards for the treatment of acute GVHD rely primarily on steroids alone as initial therapy and reserve additional agents for steroid refractory disease. Previous studies in steroid refractory GVHD have shown that anti-TNFα agents have significant efficacy but the majority of patients still die from GVHD or its complications. Our results show that the combination of etanercept plus steroids as initial treatment for GVHD results in significantly better CR rates four weeks later compared to steroids alone. These CRs were durable and could not be explained by differences in the steroid dose at four weeks. Of note, etanercept plus steroids improved the outcome for recipients of both related donor and unrelated donor transplants which translated into significantly improved survival at six months for unrelated donor transplant recipients. The improvements in outcome were realized without an increased incidence of serious infections, chronic GVHD or relapse.

Animal studies have demonstrated that TNFα plays a critical role in both the gastrointestinal tract[18,19] and the skin, but its role in the liver is more controversial. Our data confirm mechanistic studies of GVHD pathophysiology in animal models that have delineated both TNFα dependent and TNFα independent pathways of disease because TNFα inhibition increases response rates but does not completely eliminate GVHD. All patients who received etanercept also received steroids, and therefore the relative importance of these pathways in clinical GVHD remains to be determined in future studies.

One potential concern regarding the use of TNF-inhibitors to treat GVHD is an increased risk of infections, particularly mycobacterial and fungal infections. Invasive Aspergillus infections have been associated with use of the anti-TNFα monoclonal antibody infliximab for treatment of GVHD in two retrospective studies involving a total of 32 patients. Although the overall incidence of infection was significant—as would be expected in patients with GVHD receiving high dose steroids—we did not observe any significant difference in infection rates, including fungal infections, in patients also treated with etanercept. The discrepancy between the two studies may be due to potential differences in the mechanism of action of the two drugs: infliximab can induce systemic elimination and clearance of monocytes and macrophages that express membrane-bound TNFα, whereas etanercept does not. In addition, the recent availability of more effective prophylactic agents against a broad range of fungal species may have contained the overall infectious risk. We also did not observe increased morbidity and mortality from etanercept in patients who developed gram-positive infections, which differs from prior reports in other disease settings.

If these data are confirmed in other multi-center trials, we may well be able to use inhibition of TNF-α as an important adjunct to therapy for GVHD that one day may be able to reduce or even eliminate the need for prolonged high-dose steroids in some patients.

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Новый подход к терапии острой болезни «трансплантат против хозяина»

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Резюме

Болезнь «трансплантат против хозяина» (РТПХ) является основной причиной заболеваемости после аллогенной трансплантации гемопоэтических стволовых клеток (алло-ТГСК). Многочисленные доклинические исследования показали, что фактор некроза опухолей (TNFα) представляет собой важный эффектор РТПХ в условиях эксперимента. Стандартная терапия острой РТПХ с применением высоких доз стероидных гормонов приводит к полному клиническому ответу у 35% больных. В то же время у больных, леченных препаратом «этанерсепт» и стероидами, чаще достигался полный клинический эффект, нежели у больных, леченных лишь стероидами (соответственно, 69% и 33%, P=0,0001). Это различие наблюдалось у реципиентов при ТГСК как от родственных, так и неродственных доноров. Уровни TNF R1 (биомаркера активности РТПХ) в плазме были повышенными в начале РТПХ и значительно снижались только у больных с полным клиническим ответом на лечение. Делается вывод о том, что этанерсепт в комбинации со стероидными гормонами в качестве исходной терапии острой РТПХ приводит к значительному возрастанию частоты полного клинического эффекта от лечения. Таким образом, медикаментозная блокада цитокинов может в будущем стать важным элементом лечения РТПХ.

Ключевые слова: трансплантация костного мозга, болезнь „трансплантат против хозяина“, РТПХ, воспалительные цитокины, фактор некроза опухолей-альфа, стероиды