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Systemic treatment of chronic GVHD

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Abstract

Severe chronic graft versus host disease (GVHD) is the main factor for late morbidity and mortality in long-term survivors after allogeneic hematopoietic cell transplantation. The only established treatment of chronic graft versus host disease is the use of high dose corticosteroids. However, multiple different treatment approaches have been evaluated mostly in small phase 2 studies. These included calcineurin inhibitors for blocking T-cell activation, classical cytotoxic drugs, like methotrexate or azathioprine, as well as immunomodulatory substances like cytokine inhibitors or thalidomide. More recently novel treatment approaches have been evaluated. These include the use of B-cell antibodies and the tyrosine kinase inhibitor imatinib. Furthermore treatment options beyond mere immunosuppression that aim to induce tolerance are currently under investigation. These include extra-corporal photopheresis and treatment with inhibitors of the mammalian target of rapamycin. This review will discuss these different treatment approaches.

Keywords: chronic GVHD, calcineurin inhibitors, mTOR, extracorporal photopheresis, immunomodulatory drugs, steroids, methotrexate

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is the treatment of choice for high risk hematological malignancies. Its success, however, is hampered by high treatment associated mortality, mostly due to acute and chronic graft versus host disease (GVHD).

Although mild chronic GVHD may improve survival in patients with malignant diseases and usually needs no therapeutic intervention, severe chronic GVHD has devastating effects on multiple organs and significantly contributes to late morbidity and mortality in long-term survivors after allogeneic HCT [1]. The only established treatment of chronic graft versus host disease is the use of high dose corticosteroids. This therapy, however, is associated with multiple adverse reactions including life threatening infections, and moreover not all patients respond to this treatment approach. Therefore alternative treatment options are urgently needed.

Calcineurin inhibitors

In 1988 Sullivan introduced a new alternating-day regimen of prednisone (1 mg/kg every other day) and oral cyclosporine (6 mg/kg every 12 hours every other day) for patients with high-risk extensive chronic GVHD (thrombocytopenia < 100.000/ μ l) as primary treatment, and achieved with this approach a remarkable 4-year survival of 50%. The overall response rate after 9 months was 56%, and there were 17% treatment failures. The relapse risk was 23% and the mortality 47% [2]. These results were strikingly better when compared to an earlier study where using steroids alone for patients with these disease characteristics resulted in a 5-year survival of only 26% [3]. For many years the combination of cyclosporine and prednisolone was regarded as standard primary treatment of chronic GVHD [4]. However, a more recent large randomized clinical trial comparing the combination therapy with prednisolone monotherapy revealed no difference in the major endpoints therapy-related mortality, overall mortality,

need for secondary treatment, or discontinuation of all immunosuppressive therapies. However, disease-free survival was significantly worse in the combination arm, suggesting a destructive effect of cyclosporine on the graft-versus-leukemia effect [5]. Although this study was performed in patients without thrombocytopenia, it nevertheless did not substantiate the hypothesis that the administration of cyclosporine reduces transplantation-related mortality among patients with chronic GVHD.

Another calcineurin inhibitor used in transplantation is tacrolimus. However, data on its use in chronic GVHD is scarce. Its efficacy as salvage therapy in chronic GVHD was evaluated in a small phase 2 study. Although 13% of patients achieved complete remission of GVHD and could discontinue tacrolimus, a failure rate of 79% is not very encouraging. Nevertheless, it might be of benefit in some selected patients [6].

Cytotoxic drugs (MTX, Cytoxan, Azathioprine, MMF, Pentostatin)

Since low-dose methotrexate (MTX) has been proven to be effective in the prophylaxis of acute GVHD and has low toxicity profile as well as being a cost effective alternative, it has been evaluated in a series of small retrospective analyses for the treatment of chronic GVHD [7-10]. The response rates varied from 59–76%, thus suggesting methotrexate in doses of 7.5 to 15 mg to be active in chronic GVHD. Best responses have been seen in lichenoid, cutaneous, and gastrointestinal chronic GVHD. Consequently, low-dose methotrexate should be evaluated in prospective clinical trials.

Another cytotoxic drug evaluated in a small patient series for the treatment of chronic GVHD is cytoxan. It was used as pulse therapy (1000 mg/m²) and the response was dependent on the organs involved, with best responses seen in skin and mucous membrane GVHD. Remarkably, 80% of patients with liver GVHD also responded to this treatment [11,12].

The use of azathioprine in addition to prednisolone has been evaluated in a randomized trial in patients with chronic GVHD without thrombocytopenia [3]. No benefit could be observed by the addition of azathioprine. On the contrary, in the combination arm the non-relapse mortality doubled and overall survival decreased from 61% in the prednisolone arm to 47% in the prednisolone plus azathioprine arm. Therefore for treatment of chronic GVHD no role for azathioprine has been as yet established.

The more lymphocyte-selective purine antagonist mycophenolate mofetil (MMF) has been studied in a small prospective and several small retrospective studies for treatment of refractory chronic GVHD [13-15]. The response rates varied from 64–100% depending on organ involvement, with best responses seen in cutaneous manifestations. Generally the drug was well tolerated and a steroid sparing effect was observed in most studies. However, infectious complications seemed to be increased. A recent prospective randomized trial for initial treatment of chronic GVHD has been closed prematurely, as an interim analysis showed no benefit of adding

MMF to standard treatment [16]. Therefore MMF should not be added to the initial systemic treatment regimen for chronic GVHD. Nevertheless MMF can be considered for secondary treatment of refractory patients.

Georgia Vogelsang has evaluated the purine analog pentostatin in a prospective phase 2 trial for treatment of steroid-resistant chronic GVHD [17]. Pentostatin was administered at a dosage of 4 mg/m² every other week for a minimum of 24 weeks. Although most patients had failed more than one prior immunosuppressive regimen (median 4), 55 % of the patients had an objective response and survival at 2 years was 70%. Responses were best in lichenoid skin GVHD. Of the 32 responders 8 went off the study because of adverse events. Infections were the most significant toxicity.

Thoraco-abdominal Irradiation

Low dose thoraco-abdominal irradiation (1 Gy) was applied by the group of the Hospital Saint-Louis in Paris to 41 patients with refractory extensive chronic GVHD [18]. Eighty-two percent of the patients achieved a clinical response, and two years after the irradiation 25% of the patients had a complete response. Best responses were seen in patients with fasciitis (79%) and oral GVHD lesions (73%). However, one third of the responders responded only temporarily. The major adverse event was mild pancytopenia. Especially in patients with fasciitis and oral GVHD lesions low dose thoraco-abdominal irradiation may be considered as a safe and efficient treatment option.

Immunomodulatory drugs

Thalidomide was first reported in 1992 to be active in chronic GVHD [19]. In the following years a couple of retrospective studies seemed to confirm its efficacy with response rates between 36 and 75% [20-22]. However, two randomized trials failed to prove any benefit of adding thalidomide to standard treatment of extensive chronic GVHD [23,24]. The Seattle trial could not even evaluate the efficacy since more than 90% of the patients discontinued the study drug before resolution of GVHD, because of severe neutropenia and neurological symptoms. Therefore the use of thalidomide can not be generally recommended. However, selected patients may benefit from low dose thalidomide (100–200mg/d).

Clofazimine, a drug with activity in leprosy and various chronic autoimmune skin disorders, has been reported to be active also in chronic GVHD in a small phase 2 trial [25]. It was given orally once a day at a dose of 300 mg for 90 days and at a dose of 100 mg thereafter. More than 50% of the patients with skin involvement, contractures or oral GVHD manifestations achieved responses. The most common side effects were gastrointestinal and hyperpigmentation. Therefore clofazimine appears safe and, maybe, efficacious. However, the results of this small study are still to be confirmed in larger trials.

The malaria drug hydroxychloroquine is supposed to interfere with antigen presentation and has synergistic activity with calcineurin inhibitors in vitro. Therefore it has been evaluated for treatment of chronic GVHD in a small phase 2 trial [26]. Forty patients with steroid resistant or dependent

chronic GVHD were treated with 12 mg/kg/day with an overall response rate of 53%. In all responders steroids could be tapered to at least 50% of the initial dosage. There were no major toxicities. While this study also awaits confirmation in larger trials, the use of hydroxychloroquine as prophylaxis for chronic GVHD revealed disappointing results in a randomized double blind clinical trial [27].

Cytokine modulation may be another treatment option to treat chronic GVHD. And, indeed, there have been anecdotal reports on the use of soluble tumor-necrosis-factor receptor [28,29] or of antibodies against the interleukin-2 receptor [30,31] for treatment of chronic GVHD. With patient numbers between 4 and 10 the response rates varied from 50% to 75%.

Two recent small clinical studies have suggested the tyrosine kinase inhibitor imatinib mesylate to be active in the treatment of steroid-refractory sclerodermatous GVHD, via inhibition of fibroblast activity and TGF- β [32,33]. Response rates of 50–79% have been reported. However, especially at higher doses, up to 30% of patients did not tolerate imatinib and stopped treatment.

Rituximab

As B-cells are involved in the pathophysiology of chronic GVHD via production of allo- and auto-antibodies it seems reasonable that the B-cell specific monoclonal antibody rituximab may be efficacious in the treatment of chronic GVHD. Several studies have addressed the role of rituximab in the treatment of chronic GVHD [34-37]. The overall response rates varied from 50–80%. Organ-specific response rates were 13 to 100% for involvement of the skin, 0 to 83% for involvement of the oral mucosa, 0 to 66% for involvement of the liver, and 0 to 38% for GVHD of the lung.

Extracorporeal photopheresis (ECP)

In ECP a small part of the patient's mononuclear cells are exposed to the photosensitizer 8-methoxypsoralen and irradiated with ultraviolet A light extra-corporally. The irradiated T-cells undergo apoptosis and the apoptotic cells are reinfused into the patient, and it has been suggested that secondarily tolerogenic antigen-presenting cells (APCs) are induced. Therefore ECP therapy, unlike other immunosuppressive regimens, does not cause global immunosuppression, but induces immune tolerance. Recent clinical and animal studies demonstrate that ECP therapy induces antigen-specific regulatory T cells, including CD4+CD25+FoxP3+ T cells and IL-10-producing Tr1 cells [38]. The clinical use of ECP to treat chronic GVHD was pioneered by Hildegard Greinix in Vienna [39]. In 15 patients ECP was well tolerated and achieved complete responses in 80 percent of cutaneous manifestations and 70% for liver involvement. Subsequently ECP was evaluated in a number of clinical trials [40-45]. In general, skin manifestations including sclerodermatous lesions responded best to ECP and occasionally it was also reported to improve pulmonary manifestations of chronic GVHD [46]. In a recent randomized multi-centre trial the addition of ECP to the standard treatment seemed to be more effective even in sclerodermatous skin disease with a 40% response rate at 12 treatment

weeks, although the primary endpoint, blinded assessment of skin score, did not reach a significant level [47]. However, a clear steroid sparing effect could be demonstrated.

Inhibitors of the mammalian target of rapamycin (mTOR-I)

Sirolimus and everolimus, inhibitors of the mammalian target of rapamycin (mTOR-I), combine immunosuppressive properties with antiproliferative effects on fibroblasts and smooth muscle cells [48]. mTOR-I exert their action by binding to FK-binding protein 12 (FKBP12), and subsequently forming a complex with the mammalian target of rapamycin (mTOR) and the raptor/riCTOR proteins. The generation of this complex results in cell cycle arrest in G1 via inhibition of DNA transcription, DNA translation, and protein synthesis. In contrast to CNI, sirolimus promotes the generation of CD4+CD25+FoxP3+ regulatory T-cells [49]. These data indicate that mTOR-I could provide additional advantage for the treatment of chronic GvHD both because of their antifibrotic activity and by possibly inducing tolerance. The mTOR-I sirolimus and everolimus have been extensively studied as immunosuppressants in solid organ transplantation. Substituting CNI with mTOR-I seems to overcome long term threats, like chronic allograft dysfunction and vasculopathy after solid organ transplantation [50]. In allogeneic hematopoietic cell transplantation, mTOR-I have demonstrated efficacy in prophylaxis and treatment of acute GVHD in a number of studies [51,52].

However, considerable toxicity like transplant associated microangiopathy has been observed when mTOR-I were used in combination with CNI, which could be avoided in a CNI-free regimen [53]. Sirolimus has also been evaluated in second line treatment of chronic GVHD in small phase 2 trials mostly in combination with CNI [54-56]. The response rates varied between 56% and 81%. Major adverse events were hyperlipidemia, renal dysfunction, cytopenias and transplant-associated microangiopathy, which lead to termination of therapy in up to 1/3rd of treated patients. These experiences prompted us to avoid the combination of CNI and mTOR-I in the treatment of chronic GVHD. Intriguingly, when analyzing our data on the use of mTOR-I in sclerodermatous chronic GVHD, similar efficacy was achieved despite the absence of calcineurin-inhibitors (CNI). Compared with a study describing the treatment of chronic GVHD with sirolimus in combination with tacrolimus and corticosteroids we achieved similar response rates (76% in our study vs. 73% reported by Couriel et al.) and a more favorable toxicity profile [57]. Importantly, in contrast to the use of CNI, no increased relapse rate has been observed. This suggests that the graft versus leukemia effect is not compromised by mTOR-I therapy but may be even facilitated by the antitumoral activity of mTOR-I [58]. No differences were seen between sirolimus or everolimus treated patients. Importantly, in our study, we observed no nephrotoxicity and TMA was rare (5.9%), correlating with high trough levels of mTOR-I. Generally, if low therapeutic trough levels (4–8 ng/ml) were maintained, toxicities associated with mTOR-I therapy were moderate. Since mTOR-I possibly interfere with wound healing [59], they should be used with caution in patients with cutaneous or mucosal ul-

cers. In case of progressive ulcerous lesions, other therapeutic modalities should be chosen (e.g. extracorporeal photopheresis). mTOR-I seem to enhance plasmatic coagulation, as suggested by significant shortening of prothrombin time in a significant number of patients. Therefore, plasmatic hemostasis markers should be monitored during mTOR-I therapy and antithrombotic prophylaxis should be considered, especially if patients have additional risk factors, e.g. steroid therapy. The involvement of mTOR in coagulation signaling cascades has as yet not been reported. Thus, further experimental studies are needed to clarify the possible role of mTOR-dependent downstream pathways in hemostasis. Hyperlipidemia was frequent, but seldom required therapeutic intervention. Similar results were observed in another CNI-free trial for the treatment of chronic GVHD utilizing everolimus in combination with steroids and in part with azathioprine [60]. Taken together mTOR-I appear to be an effective treatment option for chronic GVHD with a low toxicity profile as long as low therapeutic drug trough levels are maintained and combination treatment with CNI is avoided.

Conclusion

Severe chronic graft versus host disease remains the main factor for late morbidity and mortality in long-term survivors after allogeneic hematopoietic cell transplantation. The only established treatment of chronic graft versus host disease is the use of high dose corticosteroids, which is associated with multiple adverse reactions. Despite a myriad of alternative or additive treatment options up to date no clear strategy to treat chronic GVHD has been established. A better understanding of the pathophysiology of chronic GVHD may guide us in the future to a more sophisticated treatment strategy. Moreover, current available treatment options have to be evaluated in controlled prospective clinical trials. The NIH consensus of diagnosis and staging of chronic GVHD provides the tools for standardized evaluation of different treatment strategies. Most currently available treatment options rely on intensification of immunosuppression at the cost of a higher infection and possibly also a higher relapse rate. However, treatment options focusing on the induction of tolerance have emerged in recent years. While preserving the graft versus leukemia effect, both the use of ECP and the introduction of mTOR-I in the therapy of chronic GVHD have been associated with enhanced formation of regulatory T-cells, thus indicating a tolerance inducing effect.

It seems to be the time to shift the paradigm of treating chronic GVHD from mere immunosuppression to more sophisticated strategies.

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Системное лечение хронической РТПХ

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Резюме

Тяжёлые формы реакции «трансплантат против хозяина» (РТПХ) являются основной причиной заболеваемости и смертности у длительно живущих больных после трансплантации аллогенных гемопоэтических клеток.

Единственный общепризнанный метод лечения РТПХ подразумевает применение высоких доз кортикостероидов. Однако другие многочисленные подходы были апробированы лишь в непродолжительные сроки на 2-й фазе клинических испытаний. Они касались ингибиторов кальциневрина для блокирования

активации Т-клеток; классических цитостатиков, например, метотрексата и азатиоприна; а также иммуномодулирующих препаратов, например, ингибиторов цитокинов или талидомида. Совсем недавно были испытаны новые лечебные подходы. Среди них применение В-клеточных антител и иматиниба (ингибитора тирозинкиназы).

Помимо этого, сейчас находятся на испытании другие лечебные методы, не исключительно иммуносупрессивного характера, но также направленные на индукцию толерантности. Для этого используют экстракорпоральный фотоферез и ингибиторы TOR (молекул-мишеней для рапамицина). В этом обзоре обсуждаются подобные лечебные подходы.

Ключевые слова: хроническая РТПХ, ингибиторы кальциневрина, mTOR (клеточные мишени рапамицина у позвоночных), экстракорпоральный фотоферез, иммуномодулирующие препараты, стероиды, метотрексат

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