REPORT

Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease

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Steroid refractory chronic graft-versus-host disease (cGVHD) is associated with a significant morbidity and mortality. Although first-line treatment of cGVHD is based on controlled trials, second-line treatment is almost solely based on phase II trials or retrospective analyses. The consensus conference on clinical practice in cGVHD held in Regensburg aimed to achieve a consensus on the current evidence of treatment options as well as to provide guidelines for daily clinical practice. Treatment modalities are the use of steroids and calcineurin inhibitors as well as immunomodulating modalities (photopheresis, mTOR-inhibitors, thalidomide, hydroxychloroquine, vitamin A analogs, clofazimine), and cytostatic agents (mycophenolate mofetil, methotrexate, cyclophosphamide, pentostatin). Recent reports showed some efficacy of rituximab, alemtuzumab, and etanercept in selected patients. Moreover, tyrosine kinase inihibitors such as imatinib came into the field because of their ability to interfere with the platelet-derived growth factor (PDGF-R) pathway involved in fibrosis. An other treatment option is low-dose thoracoabdominal irradiation. Although different treatment options are available, the "trial-and-error system" remains the only way to identify the drug effective in the individual patient, and valid biomarkers are eagerly needed to identify the likelihood of response to a drug in advance. Moreover, the sparse evidence for most treatment entities indicates the urgent need for systematic evaluation of second-line treatment options in cGVHD.

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) remains the leading cause for late morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT). Although half of the patients respond to first-line treatment, prognosis of steroid refractory cGVHD remains poor [1-3]. Primary treatment of cGVHD is based on controlled trials and consists of prednisone given with or without a calcineurin inhibitor (CNI). In contrast, evidence in steroid refractory cGVHD is limited almost

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exclusively to phase II trials or retrospective analyses. Until recently, no valid criteria for the diagnosis and staging of cGVHD severity were available, which limits the value of most reported trials on treatment of cGVHD. Moreover, most of the reported trials did not use uniform criteria for response and did not provide details on severity of cGVHD. An additional problem is the heterogeneity of the patients included in the analyses, because, for some treatment options, results in children differ substantially from results achieved in adults. Although not yet validated in a prospective fashion, the National Institutes of Health (NIH) consensus criteria on diagnosis and staging of cGVHD as well as on treatment response criteria, reported in 2005, now provide defined criteria that should improve the validity of future results on treatment of cGVHD [4-9].

The Consensus Conference on Clinical Practice in Chronic GVHD held in the fall of 2009 in Regensburg, Germany (complete program provided at www.gvhd.de), aimed to summarize the current available evidence for second-line treatment and to provide practical guidelines for the use of treatment modalities. The presented consensus was based on a review of published evidence and a survey on the current clinical practice in transplant centers from Germany, Austria, and Switzerland, with 31 of 37 centers responding to the survey. The results of the survey are shown in Table 1. Moreover, the consensus was circulated among all centers performing allogeneic HSCT in Germany, Austria, and Switzerland and was discussed during the Consensus Conference meetings. The Consensus Conference was organized under the auspices of the German Working Group on Bone Marrow and Blood Stem Cell Transplantation (DAG-KBT) and the German Society of Hematology and Oncology (DGHO), the Austrian Stem Cell Transplant Working Group of the Austrian Society of Hematology and Oncology, the Swiss Blood Stem Cell Transplantation Group (SBST), and the German-Austrian Paediatric Working Group on HSCT.

The evaluation of evidence and the subsequent recommendations were graded according to the system used by Couriel [10]. Because the evidence of the majority of treatment options in cGVHD is sparse and therefore the strength of recommendation falls into category C for most of the therapeutic options, category C and evidence III level were further specified as shown in Tables 2 and 3. Strength of recommendation and evidence levels were first rated by an expert panel and subsequently rated by all participants of the consensus process. Only evidence from the use in cGVHD was included in the evaluation. We mainly focus on reported clinical trials and retrospective analyses. The literature search was performed by the working group on second-line treatment within the Consensus conference using the Pubmed database. Only English literature was considered. Abstracts from the Bone Marrow Transplantation Tandem meetings, the European Bone Marrow Transplantation meetings, and the American Society of Hematology meetings were cited but were not included in the evidence rating.

PRINCIPLES OF SECOND-LINE TREATMENT OF CGVHD

Currently no uniformly accepted definition of steroid refractory cGVHD is available, and generally accepted criteria include (1) progression on prednisone at 1 mg/kg/day for 2 weeks, (2) stable disease on $\geq$0.5 mg/kg/day of prednisone for 4-8 weeks, and (3) inability to taper prednisone below 0.5 mg/kg/day. Treatment duration may vary depending on clinical manifestation (eg, sclerosis requires longer to respond) or toxicity of the agent (eg, shorter duration in the presence of significant toxicity) [3,7]. Although different treatment options are available for salvage therapy of steroid refractory cGVHD, the "trial-and-error system" remains to date the only way to identify the drug or drug combination effective in an individual patient. In principle, initial secondary treatment should include agents with an adequate safety profile and well-documented activity like CNI, extracorporeal photopheresis (ECP), mTOR inhibitors, or mycophenolate mofetil (MMF), whereas agents with significant side effects should be reserved to third- or fourth-line treatment. In addition, steroid sparing should be an important goal of salvage therapy of cGVHD. Because no predictors of response are yet available either for single immunosuppressive agents or combination therapies, most patients receive empirical treatment in daily clinical practice and changes of therapeutic components in case of lack of response are performed at the individual clinician's discretion. Nevertheless, at time of initiation of secondary or any further treatment, it is suggested not to change more than 1 drug at once, because adding several drugs at once may interfere with identification of the active component and might lead to prolonged use of inactive components. This does not apply to patients showing rapid progression of cGVHD, indicating complete failure of treatment, or the need to withdraw agents because of toxicity. In the presence of lack of response, continuation of at least 1 drug during the change period is suggested because there is a risk to end up with a new combination without individual efficacy, which would leave the patient without effective immunosuppression.

As in first-line treatment, response to salvage therapy should be assessed after 8-12 weeks. If patients have progression of cGVHD after 4 weeks, a new treatment option should be offered. However, patients should be exposed to therapeutic drug levels for an