ABSTRACT

Patients with chronic lymphocytic leukemia (CLL) have an indolent and protracted clinical course that must be differentiated from those who have aggressive disease progression and fatal. Younger patients with high-risk criteria may benefit from more aggressive treatment such as stem cell transplantation hemopoéticas (HSCT). Autologous presents cases with cytogenetic and molecular remission, low mortality rate, but do not show the plateau in the survival curve and high rate of relapse. Allogeneic transplants with myeloablative regimen have high rates of toxicity and mortality, but showed the graft versus leukemia effect, which increases the possibility of curing these individuals. The option of allogeneic transplants is directed to non-myeloablative conditioning regimen, which can also be applied to older patients or patients with comorbidities, and maintain the potential GVL effect. The identification of patients who may benefit from these procedures, characterize and highlight new prognostic markers remains a subject of many clinical studies and was the objective of the group responsible for discussing the guidelines of HSCT on the consensus of the Brazilian Society of Bone Marrow Transplantation - SBTMO. We therefore consider that HSCT for chronic lymphocytic leukemia (CLL) must follow, for his statement, the criteria of the European Group for Blood and Marrow Transplantation (EBMT) and if there is availability of a related donor, the option should be the HSCT with allogeneic non-myeloablative regimen. The unrelated allogeneic HSCT and autologous must be considered as secondary option of unavailability of donor, special situations and clinical trials.

Keywords: chronic lymphocytic leukemia, transplantation of hematopoietic stem cells, allogeneic, autologous, conditioning regimens, treatment.

ABSTRACT

Transplantation of hematopoietic stem cells in chronic lymphocytic leukemia, a proposal of the I Guidelines of Bone Marrow Transplantation of the Brazilian Society of Bone Marrow Transplantation, California January 2009

Hematopoietic stem cell transplantation in chronic lymphoid leukemia: A Proposal by the Brazilian Consensus on Bone Marrow Transplantation of the Brazilian Society of Bone Marrow Transplantation, California January 2009

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Patients with chronic lymphocytic leukemia usually; Have an indolent and prolonged clinical course and Need To Be Differentiated from Those Who Have an aggressive and fatal disease. Younger patients suffering from high-risk Criteria May benefit with a more aggressive treatment That includes hematopoietic stem cell transplantation (HSCT). Autologous transplantation, Despite of the Encouraging results with cases of molecular and / or cytogenetic remission and low mortality rates, does not present a plateau in survival curves and Has a high relapse rate. Allogeneic transplantsations using myeloablative regimens, Have high toxicity and mortality rates, But Also demonstrates the graft-versus-leukemia effect That Increases The Possibility of cure of These individuals. So the option of allogeneic transplants for patients suffering from CLL is directed to using non-myeloablative conditioning regimens, Which Can Also Be Applied to older Patients or Those with comorbidities, and Maintain a potential graft-versus-leukemia effect. The identification of Patients Who May Benefit From These procedures and the characterization of new prognostic markers Remain Subjects of the many clinical studies and Were The Objective of the group Responsible for discussing guidelines for CLL of the consensus on SBTMO HSCT. Thus we Believe That HSCT for CLL Should follow the Criteria of the EBMT. When a sibling donor is available the best option is allogeneic HSCT with a myeloablative regimen. The strategy "of unrelated allogeneic or autologous HSCT Must Be Considered as a second option When the donor is available, for Special Situations and clinical trials.

**Key words:** Chronic lymphocytic leukemia, hematopoietic stem cells transplantation, allogeneic, autologous; conditioning regimen; treatment.

### Introduction

Chronic lymphocytic leukemia B-type (LLC) is a heterogeneous disease often indolent clinical course, characterized by a progressive accumulation of lymphocytes, usually CD5 + lymphoid tissues, bone marrow and peripheral blood. The identification of the disease dates back to 1903, with Turk, and detailed description of the LLC in eighty cases was conducted by Minot and Isaacs in 1924. 1 CLL affects the elderly, with a median age of onset of the disease around the 65 years. Most patients are aged above 60 years, but one third of these are below this age. The occurrence of cases below 50 years is considered rare, and extremely unusual their appearance below 40 years of age. It is a type of leukemia more common in Western adults, rare in eastern and twice as common among men. 2-4 occurs about three to five cases of CLL per year for every 100 000 inhabitants. 1

The annual incidence for patients over 70 years is twenty cases per 100 000 inhabitants. There are three descriptions of increasing the number of cases of measles. This may be credited to several factors, such as the recent habit of the population to carry out periodic examinations, improvement of diagnostic resources and the change in diagnostic criteria. 5 The etiology of CLL is unknown, although there are cases in siblings, relatives and even several generations of one family. 6-8 There is no evidence of responsibility for environmental agents in the genesis of the disease (6,9) or reporting of cases exposed to ionizing radiation, 10 chemical, petroleum or carcinogens classics such as benzene. 9-11 was shown an association between CLL and the "agent orange" herbicide defoliant used during the Vietnam War from 1962 to 1971. 12 CLL express high levels of antiapoptotic proteins such as BCL family, and low levels of pro-apoptotic proteins such as BAX. None of the proto-oncogenes are usually involved in B cell malignancies, such as BCL 2, BCL 6, PAX-5 or C-MYC are changed in the LLC. 14

Cytogenetic changes are present in more than 80% of cases and associated with molecular changes confer prognostic factors that can be used in clinical practice. 15

### Prognostic factors

Prognostic factors are the classification systems of Rai and Binet, using clinical and hematological data have major importance and have the power to predict and guide the therapeutic approach (Table 1). Are prognostic factors in addition to the classification systems, the lymphocyte doubling in 12 months, 16 the histopathological pattern of marrow involvement, 17 the serum levels of β 2-microglobulin 18 C23 soluble antigen 19 and thymidine kinase. 20-21 cytogenetic changes observed in patients with CLL can be divided patients into risk groups, and certain changes may predict the patients most likely to a bad outcome. 22-25 Changes in 17p and 11q have poor prognosis, so as a tumor suppressor gene p53. 26 Amendment of p53 is considered an adverse prognostic factor for the second most important multivariate analysis in prospective and retrospective studies with patients in early stages or advanced CLL. It was observed that the incidence of abnormalities is low in asymptomatic patients in early stages of the disease, there are suggestions of early therapy in patients who are carriers of this abnormality. 27
The gene of the immunoglobulin (Ig) has an important role in the pathogenesis of the disease and rearrangements of the human variable region (VH) are considered predictors. Patients with no mutations in IgVH have a bad prognosis of patients with the mutation. Apparently there is a correlation between the alteration of IgVH mutational status and genomic aberrations. The expression of CD38 is present in a percentage around 20% of patients and those who have expressed a reduction in overall survival and an apparent correlation with the mutational status of IgVH gene. The ZAP-70 (Zeta-Associated Protein of 70kDa) is a protein kinase that is normally expressed in T lymphocytes and NK cells and is detected by flow cytometry. In patients with CLL, ZAP-70 can or may not be increased and correlated with the IgVH mutational status, disease progression and survival.

Are considered high risk, according to the EBMT, and capable of being used for the indication of HSCT or second-line therapies following criteria:

- Lack of response or early relapse within 12 months after treatment with purine analogues,
- Relapse within 24 months after purine analogue therapy combined with another drug or treatment is considered similar effectiveness as the transplantation of autologous hematopoietic stem cells.
- Deletion of p53 / del 17p13 mutation in a patient who needs treatment
- Indication of autologous HSCT should be indicated together on clinical protocols.

**Method**

For these data was performed a literature search in Medline and Clinical Trials at the National Institute of Health, USA, following the guidelines of the organization of consensus SBTMO of BMT.

All participants had equal participation in drafting this document, and this is the final version adapted after the first meeting of guidelines on bone marrow transplantation in Rio de Janeiro in June 2009.

Following we will discuss the various methods of transplantation, conditioning regimens, the results and current status of HSCT.

**Transplantation of autologous hematopoietic stem cell**

Studies have demonstrated achievement of clinical and molecular remission with autologous HSCT in CLL patients at high risk or refractory to conventional treatments. The results are observed in single-arm studies or comparative, not randomized, and therefore limited. There are no publications of prospective controlled studies comparing autologous HSCT versus chemotherapy. None of these studies also failed to demonstrate a plateau in the curves of overall survival. The feasibility of HSCT has been
demonstrated since 1993 when twenty patients were evaluated for CLL patients at high risk, conditioned with total body radiation (TBI) and cyclophosphamide, as a result, received salvage autologous cell purged with monoclonal antibodies, or receiving ransom allogeneic T cell-depleted. The results were: complete remission (CR) in 89% and low transplant related mortality (MRT) showing that the procedure was safe and, thereafter, should be considered as another treatment option for CLL. 40

Study of "cohort" European 38 demonstrated improved survival in high risk patients undergoing autologous HSCT compared to a group treated only with conventional chemotherapy, which offered the conclusion that this treatment option could offer better prospects to these individuals. Many questions arose, such as setting the best time to indicate the HSCT, recovery of prognostic factors that actually have meaning to those statements, and what are the best conditioning regimens. Another question would be to determine the role of purging both in vivo and in vitro, and how these patients should be followed and monitored after the procedure. European analyzes emphasize the indication of autologous HSCT earlier, thereby avoiding the adverse cumulative effect of chemotherapy in the treatment of relapses. 41,42 Most of these publications have relatively short follow-up and are more directed towards the evaluation of MRT of autologous HSCT. The development of secondary myelodysplasia, acute myeloid leukemia, or solid tumors in a short period of follow up, are factors of concern particularly in protocols involving TBI and considering that the LLC, in general, has long natural course. 43-46

Transplantation of hematopoietic stem cell myeloablative allogeneic

The main objectives of allogeneic HSCT in patients with CLL are:

- Infusion of healthy cells (not cancer) from healthy donors also.

- Obtaining the immunological effect of graft versus leukemia (GVL), and thus decrease the number of relapses.

However, this procedure has a high morbidity rate, and MRT is high, mainly due to old age observed in most patients with CLL, 47 secondary infections and graft versus host disease (GVHD). European registry data indicate an MRT of 46% and mortality secondary to GVHD 20%. 48 These figures are similar to that observed at the Fred Hutchinson Cancer Center, where mortality was not associated with recurrence was 57% (first hundred days) mainly in patients who received conditioning with busulfan. 49 Data from a Canadian publication also highlights a potent GVL effect in patients with GVHD (acute and chronic).

There is also no prospective randomized controlled studies comparing autologous HSCT vs. allogeneic HSCT. Study of the MD Anderson Cancer Center demonstrates better results than allogeneic HSCT, with the induction of more prolonged remissions even in patients with refractory disease. 50 Although the relapse rates are lower, the survival of patients undergoing allogeneic HSCT (particularly in transplants that had not kin) is mainly reduced by the toxicity of the procedure in patients with advanced age, in high-risk disease or refractory. These data support the need for use of conditioning regimens with lower doses of chemotherapeutic agents while maintaining the goal of preserving the GVL effect. 47

Allogeneic non-myeloablative or reduced intensity

The possibility of drastic reduction of the high MRT of allogeneic HSCT, keeping the grafting of the donor cells can be achieved by decreasing the doses of agents participating in conditioning regimens, although data are still coming from the few clinical trials. The authors saw that the initial transplant of hematopoietic stem cells in allogeneic non-myeloablative reduced intensity (RIC) could be applied to patients with more advanced ages. Thus, more complete data were observed in a larger number of patients with CLL. The studies are listed in Table 2.

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LLC: Leucemia linfocitica crônica; RIC: regime de intensidade reduzida; N: Número de pacientes; TRM: mortalidade relacionada ao transplante; S: sobrevida global; PFS: sobrevida livre de progressão; %. percentual

Although most patients who entered these studies had several previous treatments, most patients were consistently associated with high grafting percentages of complete remission. It is believed that the GVL effect is most responsible for the eradication of
minimal residual disease observed in these patients. The number of complications was higher in patients undergoing unrelated, but the numbers were higher percentages of complete remission, with the lowest relapse, suggesting an effective GVL in these patients. Factors considered at high risk of relapse were: low level of donor chimerism on day +30, refractory disease, high number of prior chemotherapies and adverse cytogenetics. Therefore, we conclude that the ICN has the potential to induce effective remissions in CLL patients with high risk.

Use of monoclonal antibodies in RIC

The use of monoclonal antibodies in these procedures is intended primarily to reduce GVHD without compromising the GVL effect. Promising results were obtained at MDAnderson Cancer Center with the addition of rituximab to the conditioning (fludarabine and cyclophosphamide).

But the use of alemtuzumab in conditioning, but with greater antitumor activity, showed a delayed engraftment and increased infectious complications with high mortality rates without an augmentation of the GVL effect.

Recommendations

The acquisition of hematologic remission clinical cytogenetics and molecular treatment goal LCC. The allogeneic HSCT is considered, even with the emergence of new effective medications, as the only curative therapy for patients with CLL. The BER is an option for a larger group of younger patients with refractory or risk criteria by markers (risk) biochemical, cytogenetic or molecular. The autologous HSCT should be included in the therapeutic arsenal for patients who have no donor, but who have cardiovascular risk factors such as consolidation treatment protocols in clinical studies. The presence of minimal residual disease can be confirmed with the detection of gene rearrangements of IGVH and ZAP70, and they are considered as criteria to determine the election outcome. Monitoring these patients should be periodically and cover, in addition to clinical data and hematological and cytogenetic studies of bone marrow immunophenotyping.

References


58. [ Links ]


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