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HSCT FOR CHRONIC LYMPHOCYTIC LEUKEMIA

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INTRODUCTION

Chronic Lymphocytic Leukemia (CLL), the most common leukemia in adults, is characterized by a clonal expansion of mature B cells that express CD5. It is probably one of the onco-hematological disease that has advanced the most in recent years[1]. As usual, therapeutic advancement occurs as a result of progressive biological knowledge of the disease. In this regard, in the last decade, we have learned a lot about its pathogenesis, including the identification of recurrent mutations and the clarification of clonal architectures, analysis of transcriptomes and the several stages of the leukemogenic process. These biological characteristics make it possible to classify a CLL into different risk groups and make the therapy more "intelligent"[2]. Rapidly, we evolved from conventional chemotherapy to most effective treatments, such as monoclonal antibodies, especially anti-CD20 of the first and second generations, target drugs that interfere with the signaling pathways of B cell receptors (BTK[3–6] and PI3K inhibitors7) and drugs that inhibit anti-apoptotic protein BCL-2[8,9].

Current treatment strategies include the combination of chemotherapy (chlorambucil, fludarabine and cyclophosphamide, or bendamustine), with anti-CD20 monoclonal antibodies (rituximab or obinutuzumab), BTK inhibitors (ibrutinib and acalabrutinib), the PI3K inhibitor idelalisib, and the anti BCL2 inhibitor, venetoclax. Worldwide, chemoimmunotherapy has progressively lost space for new therapies that show improved response duration and progression-free survival (PFS), in addition to the better profile of adverse events[10]. B-cell receptors inhibitors achieve high response rates but are used as a continuous treatment (until progression or intolerance), while BCL-2 inhibitors strategies induce deeper responses and are usually part of finite therapies.

Despite the progress with a significant improvement in progression-free survival with the new agents, CLL remains an incurable disease in most cases. The disease often relapse relatively early and progressively becomes refractory. Besides, in some cases, Richter's transformation occurs and outcome of this serious complication is usually dismal.

Allogeneic hematopoietic stem cell transplant (allo-HSCT) has been used less and less, but it is still an alternative to be discussed, especially in countries where the availability of new drugs is limited. Previous series have demonstrated encouraging results with a progression-free survival (PFS) of around 40-50% and overall survival (OS) of around 50-60% at 5 years. [11,12]

New alternatives of treatment, such as CAR-T cells, are also being tested for refractory patients after several previous treatment lines, and will be further discussed in this chapter.

WHEN TO PERFORM ALLOGENEIC STEM CELL TRANSPLANT FOR CLL

In 2007, an EBMT consensus of allo-HSCT for the treatment of high-risk CLL patients was proposed[13]. At that time, allo-HSCT became the treatment of choice for this group of patients. However, the treatment of CLL has changed over the last decade due to the development of new and very active agents8,[14,15]. However, there are no randomized clinical trials that compare the outcomes of allo-HSCT with conventional chemoimmunotherapy, or novel non-chemotherapy-containing regimens so far.

In this setting, there has being a great paradigm change on who, and especially when, a patient would

be a suitable candidate to an allo-HSCT. The approval of novel agents has had an impact on the role of allo-HSCT in CLL and, since the approval of ibrutinib, idelalisib, and venetoclax in the United States and Europe, the number of transplants continues to decrease (Figure 1). This trend is likely to continue as other new agents are approved and the existing approved agents are used earlier in the course of the disease 12. The same pattern seems to occur in Brazil, although slower, considering the delay on the approval of the new agents. It is important to note the great heterogeneity of the availability of the new agents in different treatment centers in Brazil, leading to a great variability on the time of transplant indication

FIGURE 1 - Allogeneic hematopoietic stem cell transplant for CLL by year

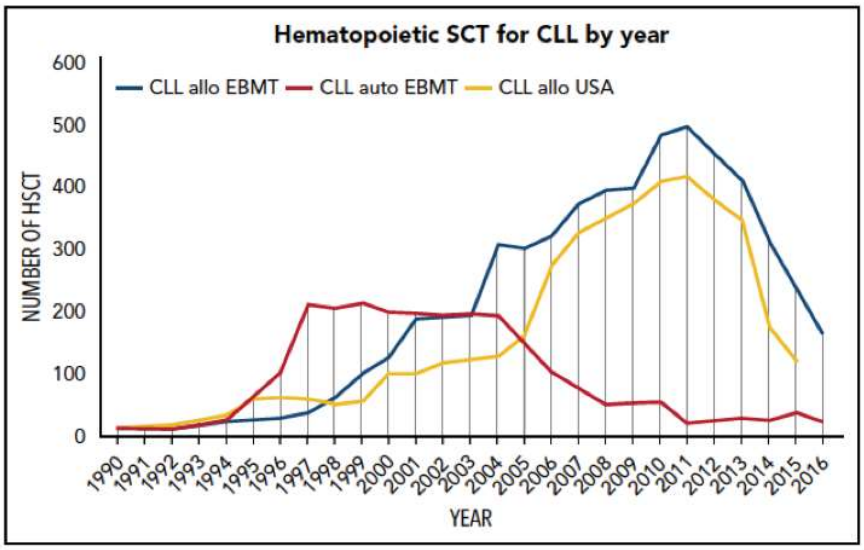


Figure 1. Changing patterns over time of HSCT in CLL in the US and Europe

The Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia of the American Society for Blood and Marrow Transplantation[16] is one of the most comprehensive guidelines on HSCT for CLL. In order to define recommendations regarding the most appropriate time for HSCT for CLL, it is mandatory to describe when in the disease therapy timeline should the HSCT be proposed.

RECOMMENDATIONS

Patients to be considered for allo-HSCT:

A.Standard Risk CLL (patients **without** del[17]p and/or TP53 mutations and/or complex karyotype): when there is lack of response or disease progression after BCR inhibitors or BCL-2 inhibitors.

B.For High Risk CLL (patients with del17p and/or TP53 mutations and/or complex karyotype):

1.Patients that experienced objective response to after BCR inhibitors or BCL-2 inhibitors after 2nd line treatment

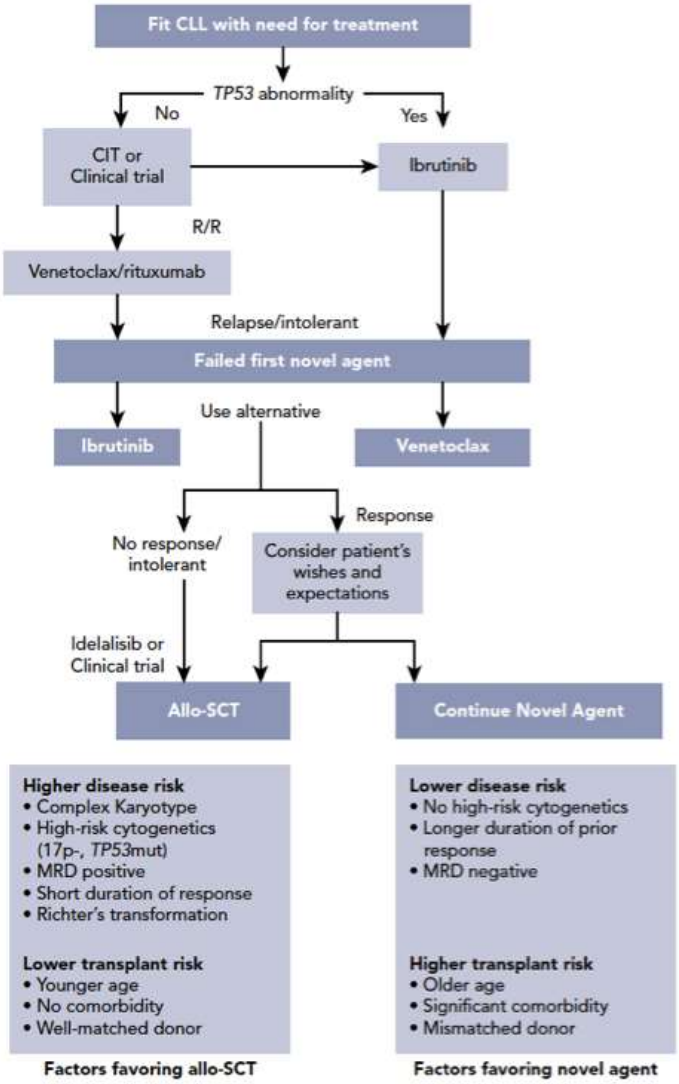
2.Patients with relapsed / refractory disease after treatment with BCR inhibitors or BCL-2 inhibitors after 2nd line treatment

3.Patients experiencing Richter transformation after achieving an objective response to therapy.

The considerations above may depend on the availability of new agents at different Brazilian treatment centers.

In 2018, Dr. John Gribben published recommendations on how and when an allo-HSCT should be performed considering the novel agents including ibrutinib, acalabrutinib, idelalisib, and venetoclax[12]. His approach led to the algorithm shown in Figure 2. Patients that require treatment and do not have TP53 mutation are candidates for chemoimmunotherapy or a clinical trial. Those patients with TP53 mutation are candidates for non-chemotherapy regimens with new agents in front line. Patients who are relapsed or refractory can be treated with BCR inhibitors or venetoclax plus rituximab. Patients who relapse or are intolerant to ibrutinib are candidates for venetoclax and those who have failed venetoclax plus rituximab are candidates for ibrutinib. Patients responding to second novel agents can either proceed to allo-HSCT or continue with the novel agent[17].

FIGURE 2 - Allogeneic hematopoietic stem cell transplant for CLL algorithm



CONDITIONING REGIMEN

There is no randomized trial comparing different conditioning regimens intensity, although myeloablative conditioning (MAC) proved to be toxic for CLL patients with high rates of transplant-related mortality since most of patients are elderly presenting great toxicity to MAC[18,19].

The reduced intensity conditioning (RIC) appears to be a more adequate regimen intensity for the CLL population. With matched sibling donors (MSD) and matched unrelated donors (MUD) the non-relapsed mortality (NRM), relapse, progression-free survival (PFS) and OS at 5 years was 23%, 38%, 39%, and 50%, respectively. The cumulative incidence of chronic extensive graft versus host disease (GVHD) was 49% for MSD and 53% for MUD. Lymphadenopathy ≥ 5cm was associated with a higher risk of relapse at 5 years (71% vs. 27%), when compared with patients without[20,21]. Allo-HSCT may overcome the poor prognosis of these high-risk genetic aberrations, including 17p deletion[22–26].

There is a great variety of conditioning regimens. The most common are: FluBu, FluTBI 200cGy[20,21], FluCy[24–26], FCR[27], and BFR[28], nevertheless, there is no comparative trial between these conditioning regimens.

RECOMMENDATIONS FOR MSD AND MUD:

A.BFR: rituximab 375mg/m^2 on day -13, and 100mg/m2 on days -6, +1 and +8, fludarabine 30mg/m^2 on days -5, -4 and -3, and bendamustine 130mg/m^2 on days -5, -4 and -3. GVHD prophylaxis with oral cyc-

losporine (CSP) starting on day -2, and intravenous methotrexate (MTX) 5mg/m^2 on days +1, +3, and + 6. In MUD will receive an additional MTX 5mg/m2 on day +11, and rabbit antithymocyte globulin 1mg/kg on days -2 and -1[28].

B.FluTBI 200cGy*: fludarabine 30mg/m^2 on days -4, -3 and -2, and TBI 200cGy on day -1. Immunosuppressive therapy starts with CSP on day -3 and oral mycophenolate mofetil (MMF) 15mg/kg tid on day +120,21. **When rituximab or bendamustine is not available,*

Allo-HSCT alternative donors are also good options for CLL. For the haploidentical donors, 2 years PFS and OS were 38 and 48% respectively[29]. Cord blood transplant is also feasible in CLL when sibling ou matched unrelated donors are absent, in a retrospective study the PFS and OS at 3 years were 54% and 45%, respectively[30].

RECOMMENDATIONS FOR ALTERNATIVES DONORS:

A.Haploidentical donors. FluCyTBI 400cGy: cyclophosphamide 14.5mg/kg on days -7 and -6, fludarabine 30mg/m2 on days -7 to -3, ant TBI 200cGy on days -2 and -1. GVHD prophylaxis: cyclophosphamide 50mg/kg on days +3 and +4, CSP starting on day +5 until, and oral MMF 15mg/kg tid starting on day +5 [31,32]. Granulocyte-colony stimulating factor (G-CSF) 5mcg/kg from day +5 until neutrophil engraftment.

B.Cord blood transplant. FluCyTBI 200cGy: cyclophosphamide 50mg/kg on day -6, fludarabine 40mg/m2 on days -6 to -2, and TBI 200cGy on day -1. For GVHD prophylaxis, we recommend CSP starting on day -3, and oral MMF 1000mg twice daily from day -3 to day +30. G-CSF 5 mcg/kg per day from day 0 until the absolute neutrophil count (ANC) was greater than 2500/mcL for 2 consecutive measurements[33].

AUTOLOGOUS STEM CELL TRANSPLANTATION

In trials comparing autologous stem cell transplantation (auto-SCT) with observation, auto-SCT improved event free survival, without benefit in overall survival, and autologous did not overcome the poor prognostic markers, in addition to worse the quality of life[34–36]. Currently, with access to targeted therapies and the small benefit of auto-SCT, this therapy is not routinely indicated in CLL.

MANAGEMENT OF RELAPSE AFTER ALLOGENEIC TRANSPLANTATION FOR CLL

Treatment of patients with relapsed CLL after allo-HSCT is a challenging unmet clinical need, particularly because patients are often refractory to chemoimmunotherapy before transplantation and, more recently, they might also be also refractory to BTK inhibitors and venetoclax. However, even in this group of high-risk patients, opportunities to achieve long-term survival remain, and the prognosis is not as bad as observed in acute leukemias or aggressive lymphomas, for example. In a retrospective analysis of 52 patients with CLL who relapsed after allo-HSCT, median OS from relapse was 35 months; and the median OS from the time of re-treatment was 21 months[37].

Relapse of CLL after allo-HSCT can be sometimes rescued by immunotherapeutic approaches, such as immunosuppression withdrawal or donor lymphocyte infusion (DLI), not all patients are responsive to these strategies. Such cases could benefit from combinations of monoclonal anti-CD20 antibodies, standard chemotherapy, and especially from targeted agents such as ibrutinib, lenalidomide, and venetoclax[37–43] In addition, promising data have emerged from several studies evaluating the effect of CAR-T cells and, more recently, CAR-NK cells for high-risk and very advanced CL[44–46]

DONOR LYMPHOCYTE INFUSION (DLI) - MRD-DRIVEN STRATEGIES

A retrospective analysis of the German Group[42] analyzed 77 consecutive allografted CLL patients for CLL in which immunosuppression tapering and rituximab-augmented donor lymphocyte infusions (DLI) were guided by MRD monitoring. Interventions started at a median of 91 (22–273) days after allo-HSCT, resulting in a probability of being event-free and MRD-negative 1 year after transplant of 57%. Patients who were event-free and MRD-negative at 12 months had a 4-year PFS of 77%. Relapse incidence post allo-HSCT was 26% at 3 years and patients who experienced relapse had a survival of 56% 2 years after relapse.

Recently, a joint French Innovative Leukemia Organization (FILO) and Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) multicenter phase II trial[47] evaluated prospectively an approach of post-transplantation MRD-driven immune-intervention for CLL that included early CsA tapering (day+90) potentially followed by DLI in case of a post-transplantation MRD positive status or keeping cyclosporine for a longer period for those with a MRD negative status. They observed relatively low rates of chronic GVHD and NRM and a very high rate of overall survival at 3 years (close to 90%). MRD negative at 12 months was achieved in 79% of evalu-

able patients. In this context of early preemptive immune-intervention, the study failed to show a benefit of DLI to convert MRD from positive to negative, although 3 out of 5 patients who received DLI were already in clinical progression at the time of infusion.

IBRUTINIB

In 2016, Ryan et al. published results of 27 patients with relapsed CLL following allo-HSCT who subsequently received ibrutinib salvage therapy and achieved an overall response rate of 87.5%, PFS rate at 2 years was 77%40.

More recently, an EBMT registry-based retrospective multicenter study included patients who underwent allo-HSCT for CLL between September 2002 and December 2015[48], and who received ibrutinib after transplantation for disease relapse. Patients in this study received a range of treatments including anti-CD20 monoclonal antibodies, DLIs, lenalidomide, standard chemotherapy and, in a small number of patients, ibrutinib. This study demonstrated that, notwithstanding high-risk disease and multiple lines of prior therapy before allo-HSCT (median 3 lines, range: 1–10), ibrutinib was an effective and tolerable salvage therapy for CLL relapse following allo-HSCT, with an OS rate at 2 years of 72% and 2-year PFS rate of 50%. Patients with late relapse after allo-HSCT (≥24 months) tended to had a superior outcome as compared to those with earlier relapses. Only 30% of patients achieved CR, as expected for a BTK-inhibitor strategy. However, among 11 patients in CR tested for MRD, 5 were negative, showing a possible ibrutinib-mediated GVL effect40,[49,50]. At the time of ibrutinib initiation, ten patients had still an active chronic GVHD, all these patients had their GVHD resolved after receiving ibrutinib and only one patient had limited de novo chronic GVHD while on Ibrutinib, with a quick resolution. Ibrutinib is indeed a therapeutic option for steroid-refractory chronic GVHD, being approved for this indication by the FDA[51–53]. Ibrutinib was well tolerated with a safety profile similar to the one observed in the overall population of patients with relapsed/refractory CLL treated with ibrutinib3. Based on this analysis, ibrutinib seems to be efficient and safe for CLL relapse after allo-HSCT, and combinations including this agent should be evaluated in larger prospective trials in this scenario.

SECOND ALLO-HSCT

The availability of new alternative therapies, including both BCR and BCL2 inhibitors have taken the place of a 2nd allo-HSCT in the relapse/refractory setting, either obviating the need for transplant or delaying this strategy until later in the management of the disease. Consequently, the number of 2nd allo-HSCT for CLL has considerably decreased, both in the United States[16] and Europe[47].

CAR-T CELLS

The first description of CAR-T cells for CLL was a clinical trial of a single infusion of allogeneic anti-CD19-CAR T cells for 10 patients with B-cell malignancies (4 with CLL) that persisted after allo-HSCT and standard DLIs. Three patients achieved durable CRs, including 2 patients with CLL. This approach is associated with significant acute toxicity, especially due to the cytokine release syndrome, but does not represent a risk for GVHD[54].

However, as more patients with CLL were included in trials with CAR-T cells, results became more disappointing. In the 134 highly pre-treated CLL patients treated with CAR-T cells reported to date, the CR rate remains of 20 to 30%, with a median PFS of 18% at 18 months55, and a proportion of the patients have a subsequent relapse at follow-up[44,56,57]

More recently, a pilot study evaluated the safety and feasibility of administering ibrutinib concurrently with CD19 CAR T-cell in 19 CLL patients. CD19 CAR T-cell therapy with concurrent ibrutinib was well tolerated; 13 patients (68%) received ibrutinib as planned without dose reduction. The 4-week overall response rate was 83%, and 61% achieved a MRD-negative marrow. In this subset, the 1-year OS and PFS were 86% and 59%, respectively, with lower CRS severity and lower serum concentrations of CRS-associated cytokines, despite equivalent in vivo CAR T-cell expansion[58].

CAR-NK CELLS

More recently, the early results of a phase 1 and 2 study of NK cells that were derived from cord blood and engineered to express anti-CD19 CAR, interleukin-15, and an inducible caspase 9 safety switch were published46. This therapy was tested in heavily pretreated patients with multiply relapsed or refractory CLL. At a median follow-up of 13.8 months, 4 of 5 patients with CLL had an objective response and 3 (67%) had a complete response. Response durations cannot be assessed because of the administration of other therapies (immunomodulatory agent, chemoimmunotherapy, or allo-HSCT), starting as early as 30 days after the infusion of CAR-NK cells. The infused CAR-NK cells persisted at low levels for at least 12 months, despite the substantial HLA mismatch between the infused NK cells and the recipient. The

inclusion of interleukin-15 in the construct may have played an important role in the persistence and anti-tumor activity of these CAR-NK cells. Allogeneic CAR-NK cells can be delivered in adoptive transfer without the serious cytokine release syndrome, GVHD, or neurologic toxic effects that have been associated with CAR T-cell therapy[59,60] Besides, this technique may become accessible to many patients with R/R CLL due to the minimal HLA-matching requirements between the donor of CAR-NK cells and the patient and the possibility to produce more than 100 doses of CAR-NK cells from a single cord-blood unit[61] .

CONCLUSIONS

Although allo-HSCT in CLL is decreasing in developing countries, in Brazil we may still consider allo-HSCT as an option in lower transplant risk patients, mainly due to inaccessibility of new agents in the public system in patients with relapse/ refractory disease. However, if new agents are available, allo-HSCT should be reserved for high-risk patients and/or relapsed / refractory disease after treatment failure with BCL-2 inhibitor and/or BTK inhibitors. Besides, clinicians should always consider including their patients in this scenario in clinical trials.

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