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Ibrutinib as a bridge to transplant in high-risk chronic lymphocytic leukemia: A case report and review of the literature

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ABSTRACT

The treatment landscape of chronic lymphocytic leukemia (CLL) has been challenged by the advent of novel classes of drugs, such as B-cell receptor (BCR)-inhibitors and BCL-2 antagonists. In selected high-risk patients, the choice to start allogeneic hematopoietic stem cell transplantation (alloHCT) or continue these agents is a matter of debate. Furthermore, published data about the impact on the feasibility of alloHCT and the optimal timing of administration are limited. Here we present a case of relapsed TP53 mutated CLL treated with ibrutinib as a bridge to alloHCT, discussing risks and benefits of different treatment options in a "real life" situation.

1. Introduction

AlloHCT has long been considered the treatment of choice for high-risk CLL. In particular, in 2007 a consensus paper established indication for alloHCT in three high-risk situations: disease refractory to purine analogs, disease relapsing within 2 years after a purine analog combination and/or disease with del(17p)/TP53 mutations [1]. The most important unfavorable prognostic factor is the del(17p)/TP53 mutation that is uncommon at diagnosis, but increases at progression/relapse (20–40%) and confers resistance to chemoimmunotherapy [2,3]. Because of the graft-versus-leukemia effect, reduced-intensity conditioning (RIC) alloHCT in CLL shows sustained progression-free survival (PFS, 35–50%) and overall survival (OS, 50–60%) at 5 years and is actually the only curative option (Table 1) [4–10]. However, despite a dramatic improvement in early death rate, non-relapse mortality (NRM) at 2–5 years continues to be high (15–30%), mainly because of complications of graft-versus-host disease (GVHD) [4–10].

New drugs recently introduced in CLL treatment are generally well tolerated and provide high response rates. In particular, the overall response rate (ORR) with ibrutinib in relapsed/refractory CLL patients is 70–90% [11–13]. Complete remissions are obtained in only a minority of patients, but the medium-term disease control seems good, with a 30-month estimated PFS rate of 69% and a 30-month estimated OS rate of 79% [13]. BCR-inhibitors are also very effective in high-risk patients with del(17p)/TP53 mutations, but survival curves in these cases seem inferiors. In a recent up-date at 5 years of experience with ibrutinib in patients with relapsed/refractory CLL, O'Brien at al. reported a median PFS of 26 months for cases with del17p and not reached for patients with no adverse genetic abnormalities [14]. A phase II trial has been specifically performed for previously untreated or relapsed/refractory patients with TP53 aberrations: among relapsed/refractory cases, 40% achieved a partial response, 40% a partial response with lymphocytosis and 20% a stable disease; the incidence of progression at 24 months was 20% [15]. Similarly, the phase II RESONATE-17 study, which evaluated ibrutinib for patients with relapsed/refractory CLL and 17p deletion, showed a 24-month PFS of 63% and a 24-month OS of 75% [16].

Current data suggest that patients with acquired resistance to ibrutinib have a poor outcome. Some series initially reported a median overall survival < 6 months, although most of these patients probably did not have the opportunity to receive newer agents [17]. At the time of ibrutinib failure, a switch to an alternate kinase inhibitor or venetoclax confers a superior PFS compared to chemoimmunotherapy [18]. The most promising data come from venetoclax, that was recently approved for treatment of relapsed patients with TP53 dysfunction, based on a phase II multicentre study by Stilgenbauer et al. [19]. A single-agent study showed an ORR of 70% among patients relapsed or refractory to ibrutinib; however, the CR rate was relatively low and data regarding long-term disease control are currently lacking [20].

Immunotherapy using T cells genetically engineered to express an anti-CD19 chimeric antigen receptor (CAR-T) is a new promising option in lymphoproliferative diseases. In a recent study, Turtle et al. reported

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Table 1
AlloHCT in CLL, main clinical trials in pre-ibrutinib era.

References	Patients n.	17p-/TP53	OS	PFS	NRM
Hahn et al. [4]	77 (57 RIC)	23/77 (36%)	63% (5 years)	48% (5 years)	22% (5 years)
Dreger et al. [5]	90	High risk (30% TP53)	58% (6 years)	EFS 38% (6 years)	23% (6 years)
Khouri et al. [6]	86	15/66	51% (5 years)	36% (5 years)	17% (1 year)
Brown et al. [7]	108 (76 RIC)	13/76 (17%)	RIC 63% (5 years) Myeloablative 49% (5 years)	53% (5 years)	16% (5 years)
Sorror et al. [8]	82	41	50% (5 years)	39% (5 years)	23% (5 years)
Schetelig et al. [9]	694	195	NR	EFS 37% (5 years)	28% (2 years)
Michallet et al. [10]	40 (40 RIC)	NR	55% (3 years)	46% (3 years)	27% (3 years)

a high rate of complete molecular remission in 24 patients (19 in progression after ibrutinib and 6 venetoclax-refractory) treated with lymphodepleting chemotherapy and anti-CD19 CAR-T cells infusion. However, 20 patients (83%) developed cytokine release syndrome and 8 patients (33%) developed neurotoxicity, with fatal outcome in one case [21].

2. Case report

F.M is a 54-year-old man affected by CLL diagnosed in February 2013 on Binet B and Rai III stages with unmutated IgVH genes and interphase fluorescence in-situ hybridization (FISH) negativity. He was also suffering from ischemic heart disease in good compensation after percutaneous angioplasty performed in 2012. Because of active symptomatic disease, the patient received six cycles of immunochemotherapy with a FCR regimen (fludarabine, cyclophosphamide and rituximab) from February to June 2013 and achieved a complete remission. In November 2014, we observed a hematologic relapse with multiple, enlarged lymph nodes in the cervical, axillary, mediastinal and abdominal area, splenomegaly and lymphocytosis, with molecular evidence of TP53 mutation. For this reason, in February 2015 he was started on ibrutinib treatment at 420 mg/day (within a Named Patient Program in Italy) and obtained a good partial remission with rapid disappearance of lymphadenopathy and splenomegaly, normalization of blood count and residual disease limited to bone marrow. Ibrutinib was well tolerated, without significant adverse events; we did not observe atrial fibrillation or bleeding, despite the use of acetylsalicylic acid. After more than 6 months of therapy, once a maximum response was achieved, we had two options: perform a consolidating alloHCT or continue on ibrutinib treatment until progression, eventually postponing alloHCT to the next treatment line. In the absence of controlled studies, there was no clear superiority of either of these two choices and we carefully discussed it with our patients. Given the poor prognosis of the disease despite the response to ibrutinib (relapse within two years after FCR and TP53 mutation) and the young age of the patient, he was assigned to alloHCT. In the absence of HLA-identical siblings, we began a research of an unrelated donor in October 2015. In February 2016, a male, 23 years old, HLA-matched donor was found. There was a bidirectional ABO-incompatibility and CMV negativity versus CMV positivity of the recipient. On 27th April 2016, the patient underwent allogeneic transplantation with peripheral blood stem cells (PBSC), preceded by a myeloablative regimen with thiotepa 5 mg/kg/d at days −6 and −5, busulfan 3.2 mg/kg/d in a single IV infusion combined with fludarabine 50 mg/m^2 at days −4, −3 and −2. The GVHD prophylaxis was based on antithymocyte globulin (Fresenius ATG), cyclosporine and a short course of methotrexate. Ibrutinib was discontinued 9 days before hospital admission. During aplasia, the patient presented mucositis of maximum grade I and two febrile episodes without microbiologic isolation. The neutrophil engraftment was observed on day +15 and platelet recovery on day +13; full-chimerism was evidenced from day +28. After discharge from hospital, there was an asymptomatic episode of CMV reactivation at 6 weeks from transplant, resolved by preemptive therapy with oral valganciclovir. To date, no acute GVHD and only a limited chronic GVHD has been observed. On July 2016, a first disease evaluation at 3 months from transplant showed a complete remission, with no lymphadenopathy or splenomegaly at CT scan, normal blood count and absence of minimal residual disease (MRD) at flow cytometry. Absence of MRD and full-donor chimerism were confirmed by a complete evaluation repeated at 6 and 12 months after transplantation.

3. Discussion

Although results with ibrutinib and other new agents are the best ever reported in patients with del(17p)/TP53 mutation, the long-term poor prognosis conveyed by these genetic abnormalities is not abrogated by these drugs [14–16]. Anti-CD19 CAR-T cells are a promising option in a near future but the complexity, cost and toxicity of this treatment are still a problem [21].

In a recent publication, the American Society for Blood and Marrow Transplantation has maintained its recommendation to alloHCT in high-risk CLL patients after failing two lines of therapy and showing an objective response to BCR-inhibitors, and in patients refractory to or progressing after BCR-inhibitors and subsequently treated by BCL-2 antagonist [22]. In a recent survey by the EBMT, Dreger et al. showed the feasibility of alloHCT after ibrutinib exposure, with a 1-year NRM of 9%; the outcome was better in ibrutinib-sensitive compared to refractory disease (1-year relapse rate 29% versus 60%) [23,24].

Our single experience confirms the results by Dreger et al. in patients who undergo alloHCT while still responding to ibrutinib. The treatment with ibrutinib has allowed us to obtain a good remission in a very high-risk case of relapsed CLL with an aggressive clinical course and TP53 disruption. Ibrutinib did not appear to adversely impact the time of engraftment, the risk of infection and the risk of GVHD. Published data are still limited about the type of conditioning regimen and the stem cell source, mostly PBSC as in our case [23,24]. We have chosen thiotepa-busulfan-fludarabine because this regimen permits a low NRM without negative impact on engraftment [25]. Our patient is still in complete remission, with no detectable MRD at flow cytometry and a good quality of life, at one year post-alloHCT.

4. Conclusion

Despite the success of BCR-inhibitors and other new agents in CLL, the alloHCT option should continue to be considered in current treatment algorithms [26,27].

The treatment choice should be based on a careful consideration of the risks and chances, taking into account individual preferences. Conditions potentially favoring the alloHCT option are: relapsed/refractory disease with TP53 aberrations, young age, absence of significant comorbidities and availability of a well-matched donor. Ibrutinib may be considered an excellent bridge to alloHCT, rather than a competing intervention, especially in CLL patients considered at high risk of recurrence, in order to achieve a long-term disease control. The

optimum timing of administration in the interrelation to alloHCT needs to be defined by additional studies.

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