Development of steroid-refractory graft-versus-host disease in a patient with Hodgkin lymphoma treated with nivolumab before allogeneic hematopoietic stem cells transplantation

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Introduction

Graft-versus-host disease (GVHD) is the most frequent complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT) and a significant cause of morbidity and mortality. Systemic steroid therapy is the basis of treatment for GVHD, however, some patients are refractory to treatment. There are concerns about an increased incidence of GVHD for patients with Hodgkin lymphoma (HL) previously treated with immune checkpoint inhibitors (ICIs). Nevertheless, later there appeared evidence that allo-HSCT can be administered fairly safe after ICIs therapy with similar GVHD data by using posttransplantation cyclophosphamide (PTCy)-based GVHD prophylaxis. However, data about patients with steroid-refractory form of GVHD in this setting is limited.

The aim of this study was to define incidence of GVHD and investigate current treatment options for patients with rrHL after bridge therapy with immune checkpoint inhibitors

Materials and methods

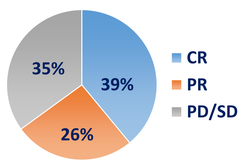
We retrospectively evaluated the results of allo-HSCT in 23 adult patients who had been transplanted at the RM Gorbacheva Research Institute, Pavlov University (CIC 725).

The baseline characteristics of the patients are summarized in Table 1.

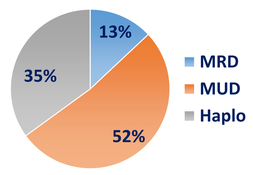
***Table 1**: Patient's characteristics*

Variable N	All the cohort (%) 23 (100)
Age, median (range)	27 (19-49)
Sex, (%) Male Female	 13 (57) 10 (43)
Number of prior therapeutic lines, median (range)	5 (3-12)
Previous autoHSCT	11 (48)
Primary resistant disease	18 (78)
Bridge therapy Nivolumab Nivolumb+ BV Nivolumab + chemotherapy	 13 (56) 5 (22) 5 (22)
Stem cell source Bone marrow Peripheral blood	 14 (61) 9 (39)
Conditioning regimen FluBe	 23(100)
GvHD prophylaxis PTCy-based GvHD	 23(100)
Median time from the last dose of ICIs to alloHSCT	83 days (range, 50-350)
Median number of nivolumab cycles	20 (range, 6-32)

Disease status



Type of donor



Disclosure of interest: none

All patients were treated with ICIs before the transplantation. Complete response to PD-1 therapy before allo-HSCT was documented in 9 patients (39%), partial response- in 6 patients (26%), 5 patients (22%) had stable disease/disease progression and 3 patients (13%) were transplanted in indeterminate response according to LYRIC criteria. All patients received reduced-intensity conditioning regimen (fludarabine 30 mg/m2, bendamustine 130 mg /m2 per day for 3 days (FluBe)) and PTCy-based GvHD prophylaxis. Three (13%) patients had matched HLA-related siblings, 12 patients (52%) had unrelated donors and 8 patients (35%) had haploidentical donors. The median time from the last dose of ICIs to allo-HSCT was 83 days (range, 50-350 days) and the median number of cycles was 20 (range, 6-32).

Results

At the time of analysis, median follow-up was 14 months (range, 1-26). Engraftment rate was 87%. The 1-year OS and EFS were 83% (95% CI, 58–93) and 74% (95% CI, 49–87) respectively, whereas the 1-year cumulative incidences of relapse and NRM were 13% (95% CI, 5–39) and 13% (95% CI, 5–38) respectively (Fig1, Fig2).

Figure 1: 1-year Overall survival

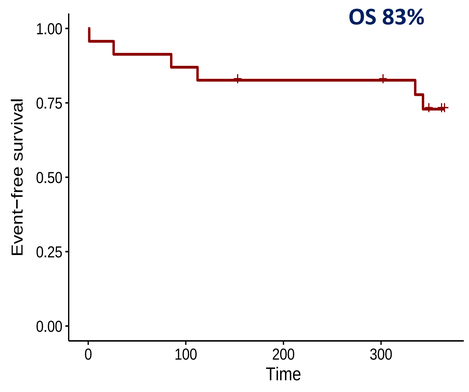
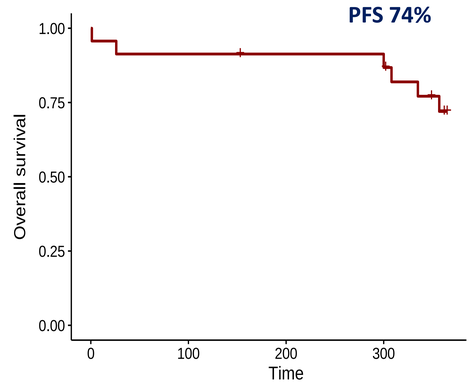
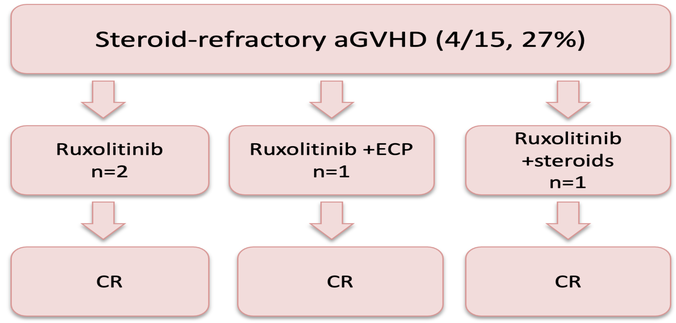


Figure 1: 1-year Event-free survival



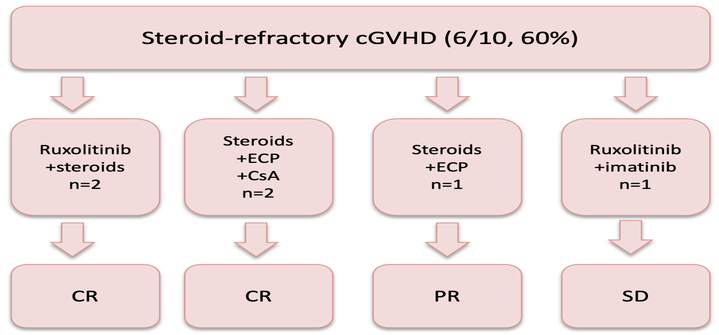
Out of the 20 patients with engraftment 15 patients developed acute GVHD including severe (grade III-IV) in 9 patients. All patients had skin aGVHD (stages 1, 2, and 3), 3 patients had gastrointestinal GVHD (stages 2, 3, and 4) and 2 patients had liver GVHD (stages 1 and 2). Four patients had a steroid-refractory aGVHD. As a second line of therapy patients received single-agent ruxolitinib (n=2) or combination of ruxolitinib with extracorporeal photopheresis (ECP) and steroids (n=2) and all patients achieved complete response (Fig3).

Figure 3: Treatment of steroid-refractory acute GVHD



Ten patients had chronic GVHD including 6 patients with moderate or severe disease. Most commonly skin (90%), mucosa (60%), gastrointestinal tract (30%), liver (20%), lung (10%) and eyes (20%) were involved. Four patients with steroid-refractory cGVHD achieved CR receiving combined immunosuppressive therapy (ruxolitinib and steroids, n=2; combination of steroids, cyclosporine A and ECP, n=2). One patient with severe skin cGVHD (score 3) achieved PR on combination of steroids and ECP, another patient with a severe refractory cGVHD (skin score 3, mucosa score 2 and lungs score 1) achieved stabilization only with third line of therapy (combination of ruxolitinib and imatinib) (Fig4).

Figure 4: Treatment of steroid-refractory chronic GVHD



Conclusions

Our study showed the trend to higher incidence of aGVHD and cGHVD including steroid refractory form after ICIs, however this did not lead to GVHD-related mortality.

Introduction of target agents for srGVHD might ameliorate GVHD-related mortality and morbidity in rrHL patients after ICIs

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