Outcomes of autologous hematopoietic stem cell transplantation in patients with refractory Crohn's disease: a single-center retrospective case series

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Abstract

Background and aims: Despite advances in biological therapies, a subset of patients with Crohn's disease (CD) remains or becomes refractory to all available treatments. Emerging evidence indicates that autologous hematopoietic stem cell transplantation (aHSCT) may offer a viable therapeutic option for carefully selected treatment-refractory CD patients.

Patients and methods: We retrospectively analyzed the outcomes of all CD patients who underwent aHSCT for treatment-refractory disease at our IBD referral center between 2011 and 2023. All included patients had severe disease, unsuitable for surgery.

Results: We included 24 CD patients (15 females, median age at transplantation 31.0 [27.0-34.5] years, median disease duration 13.0 [9.8-17.3] years) who underwent mobilization, of whom 23 patients proceeded to transplantation. All patients had CD with small bowel involvement, while 10 patients (41.7%) had concomitant perianal disease.

After a median follow-up of 114.6 [66.0-138.4] months, 8 patients (34.8%) were still in remission without need for advanced therapy. Persistent disease activity after aHSCT, defined as total SES-CD >3, occurred in 15 patients (65.2%) with median time to restarting advanced therapy of 7.0 [5.0-25.0] months.

At last follow-up, all patients are still alive. There were a few ICU admissions because of hemodynamic instability due to neutropenic fever following mobilization and transplantation. In the follow-up period, infectious complications occurred in 12 patients (52.2%).

Conclusions: Autologous hematopoietic stem cell transplantation is a safe and effective therapy for inducing and maintaining remission in carefully selected therapy-refractory CD patients after extensive multidisciplinary discussion. Although many patients didn't achieve remission, most regained response to previously ineffective therapies. (Acta gastroenterol belg., **2026,** 89**, 325-332).**

Keywords: Crohn's disease; autologous hematopoietic stem cell transplantation; efficacy; safety

Introduction

Crohn's Disease (CD) is a chronic inflammatory intestinal disorder that primarily affects the (terminal) ileum and/or colon but can involve the entire gastro-intestinal tract. It typically sets on during adolescence and is characterized by a life-long relapsing and remitting disease course with a high risk of debilitating and sometimes life-threatening complications as obstructions or intestinal abscesses that result in frequent hospitalizations, necessity for repetitive surgeries and a substantial decrease in quality of life. The last two decades have seen a significant expansion of treatment options, with biological therapies and small molecules targeting specific cytokines, cell types or pathways involved in cytokine signaling. Despite this positive therapeutic evolution, a subgroup of patients suffers from highly refractory CD where long-term remission and healing cannot be achieved and disease progresses, despite different biological therapies such as TNF-antagonists, IL12/23-antagonists, IL23-antagonists, anti-integrins or small molecules such as JAK-inhibitors (1).

The exact etiology of CD remains elusive. Genome-wide association studies have revealed over 300 susceptibility loci associated with CD with many supposedly playing a role in the innate immune system and in pathways related to autophagy, endoplasmatic reticular stress and inflammasome activation. Despite this genetic predisposition there are crucial eliciting environmental factors that are yet to be identified. There are strong indications that antigens originating from commensal bacteria are responsible for constitutively activating the adaptive immune system in predisposed individuals. A pivotal role is attributed to T-cells who lose their tolerance for certain bacterial antigens with inadequate responses and production of pro-inflammatory cytokines. Since it has not been possible to identify nor eradicate these luminal triggers up until present day, most medical therapies used for CD aim at suppressing the activation of the immune system (1).

After encouraging results in individual cases or case series hematopoietic stem cell transplantation (HSCT) is conquering its place as a treatment option for multirefractory CD patients, supposedly by rebuilding or at least thoroughly modifying the constitution of the immune system after an initiation phase of suppression caused by conditioning chemotherapy. The first suggestions that HSCT could be beneficial in CD patients came from case reports that described remission of CD in patients that had undergone allogeneic HSCT for

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hematologic malignancy. Allogeneic HSCT with healthy donor cells that do not carry the genetic predisposition to CD theoretically seems to harbor a stronger potential for definite cure of CD than autologous HSCT. However, the latter procedure in which hematopoietic stem cells of the patient self are mobilized, harvested and reinfused, gradually became the most promising of the two approaches since numerous reports described the observation of long-term remission of up to 10 years, suggesting that the treatment has a potential of resetting the immune system. Besides, autologous HSCT has a lower treatment-related morbidity and mortality when compared to allogeneic HSCT (2). In addition, there has been a growing body of evidence for the usefulness of autologous HSCT for the treatment of other auto-immune diseases like multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis and systemic sclerosis (3,4).

For a long time, the exact mechanism by which HSCT induced long-lasting remission in CD was unknown and one of the hypotheses stated was that the conditioning regime used to collect the stem cells, could on its own bring patients in deep remission, rather than the stem cell transplantation itself. The multi-center randomized clinical trial ASTIC, conducted from 2007 until 2011, subdivided 45 multirefactory CD patients to either immunoablation and autologous HSCT or deferral of HSCT for one year. Outcome analysis after one year showed that HSCT did not lead to a statistically significant improvement in sustained disease remission (comprising clinical remission, no use of corticosteroids or immunosuppressive or biological drugs and no endoscopic or radiological evidence of active disease) but there was a significant decrease in CDAI and SES-CD scores. However, HSCT was associated with significantly more toxicity (5). In 2019 the ASTIClite trial was published, where an immunoablative regimen of reduced intensity was used. Nevertheless, much more serious adverse events occurred in patients who underwent HSCT (6).

During the past years, several patients with therapy-refractory CD underwent autologous HSCT at the University Hospitals Leuven. The aim of this study is to analyze the long-term outcomes of autologous HSCT on CD disease activity and to assess toxicity related to autologous HSCT in our own patient population.

Methods

Patient selection

We retrospectively reviewed the outcome of the first 24 patients with CD that consented to undergo hematopoietic stem cell mobilization and transplantation at our tertiary referral center for IBD and HSCT between 2011 and 2023, outside a clinical trial. Inclusion and exclusion criteria were based on those of the ASTIC protocol for HSCT (5). Inclusion criteria were age between 18 and 50 years; confirmed diagnosis of active CD; unsatisfactory course despite 3 or more conventional [methotrexate (MTX), azathioprine (AZT)] or biological [infliximab (IFX), adalimumab (ADL), certolizumab (CTL), vedolizumab (VDL), ustekinumab (UST), …] therapies in addition to corticosteroids (CS); impaired function and quality of life; current problems unsuitable for surgery and patients at risk for developing short bowel syndrome. Exclusion criteria were pregnancy or unwillingness to use adequate contraception; organ failure or other severe comorbidities and concurrent infection or immunosuppressed status. Disease phenotype was classified according to the Montreal classification of CD (7). All patients had active endoscopic disease of the small bowel (with or without colonic involvement) on ileocolonoscopy (with SES-CD >3) or transmural imaging (8). Enrollment required informed consent from the patient and approval for autologous HSCT by an interdisciplinary team consisting of gastroenterologists, hematologists and surgeons.

Mobilization and collection phase

All maintenance drugs were tapered or stopped during the mobilization phase. Patients were admitted to the hospital for two consecutive days during which they received Cyclophosphamide (CPM) and Uromitexan (UMT) intravenously at a daily dose of 2 g/m^2 and 20 mg/kg respectively. Intravenous crystalloids were co-administered following an in-hospital standard operating procedure. Patients were discharged after 48 hours but asked to come back to the hospital in case of fever (defined as an one-time body temperature of more than 38.2°C or two consecutive measurements equal to or more than 38.0°C with an interval of one hour). On the sixth day after initiation patients started granulocyte colony-stimulating factor (G-CSF) at home, subcutaneously administered at a daily dose of 10 µg/kg. On the tenth day after initiation patients came back to the outpatient clinic for a CD34-positive hematopoietic progenitor cell (CD34+ cell) count on peripheral blood. If the CD34+ cell count was below 10 cells/µl G-CSF administration was continued and the patient was given a follow-up appointment at the outpatient clinic. If the CD34+ cell count on peripheral blood exceeded 10 cells/µl cytapheresis was started and continued until 3-8 x 10^6/kg CD34+ cells were harvested. Cytapheresis was completed within a maximum period of 48 hours. In one patient mobilization was done with a reduced dose of Cyclophosphamide (in accordance with the ASTIClite trial). In the last 4 included patients only G-CSF was used for mobilization, without Cyclophosphamide. The collected stem cells underwent cryopreservation with dimethylsulfoxide (DMSO) until they were thawed on the day of transplantation.

We reviewed the patients' medical records for the amount of CD34+ cells collected in every patient

and for all the adverse events during the mobilization and collection phase. Duration of neutropenia was defined as the amount of subsequent days the absolute neutrophil count (ANC) on peripheral blood was less than 500 cells/µl. Neutropenic fever was defined as an ANC of less than 500 cells/µl combined with an one-time body temperature of more than 38.2°C or two consecutive measurements equal to or more than 38.0°C with an interval of one hour. Blood culture positivity at any occasion was recorded. With regard to serious adverse events need for transfer to the ICU was reported as a separate outcome. With regard to other adverse events we chose not to specifically mention the following well-established and fully reversible secondary effects of Cyclophosphamide as outcomes unless they were refractory to all available treatments or led to complications (i.e. prolonged admission or need for transfer to the ICU): anorexia; oral mucositis; gastrointestinal symptoms (nausea, vomiting, diarrhea or constipation); asymptomatic electrolyte disturbances; myelosuppression with neutropenia, thrombocytopenia and/or anemia; transient visual disturbances and headache. Hemorrhagic cystitis, a well-established secondary effect of Cyclophosphamide, was specifically mentioned as an outcome if occurring because of its high potential for complications. As a well-established and fully reversible adverse event of G-CSF bone pain was not recorded as a significant adverse event.

Transplantation phase

All patients who continued to the transplantation phase were admitted seven days before the planned day of transplantation. They first received a conditioning regimen consisting of four consecutive days of CPM and UMT (daily doses of respectively 50 mg/kg and 20 mg/kg) and three consecutive days of rabbit anti-thymocyte globulin (rATG, daily doses of 2.5 mg/kg with every administration preceded by intravenous administration of Methylprednisolone at a dose of 1 mg/kg). On the second day after the last administration of rATG reinfusion of the autologous CD34+ cells ensued. After stem cell reinfusion measurement of the absolute neutrophil count (ANC) was performed daily on a peripheral blood sample. Starting on the fifth day after stem cell reinfusion G-CSF at a dose of 5 µg/kg was administered daily until sufficient hematopoietic recovery was achieved, defined as an ANC of more than 10.000 cells/µl.

Concerning supportive therapy we followed predefined in-hospital standard operating procedures for autologous HSCT. From start of admission until recovery from neutropenia all patients received antibacterial, antiviral and antifungal prophylaxis with oral Levofloxacin (500 mg once daily), Aciclovir (5 mg/kg three times a day) and Fluconazole (400 mg once daily) respectively. Stomach ulcer prophylaxis with Pantoprazole (40 mg once daily) was given throughout the whole admission. Preventive anti-emetic treatment with Ondansetron (8 mg two times a day) was systematically given until the day of transplantation. From start of admission until recovery from neutropenia all patients received subcutaneous Enoxaparin for prophylaxis of sinusoidal obstruction syndrome (SOS). In case of neutropenic fever intravenous Meropenem (1 g three times a day) was systematically started and oral Levofloxacin was stopped. Electrolyte levels were measured regularly (sodium, potassium, chlorine and calcium on a daily basis; magnesium twice weekly) and corrected intravenously in case of disturbances. Hemoglobin and platelet levels were measured on a daily basis and held above 8.0 g/dl and 15.000 cells/µl by administration of irradiated and leukoreduced red blood cell and platelet transfusions respectively. Patients were hospitalized and installed in a single laminar airflow room during the period of neutropenia.

We reviewed the patients' medical records for the amount of CD34+ cells reinfused in every patient and for all the adverse events during the transplantation phase. The same parameters were noted as during the mobilization and collection phase (see paragraph Mobilization and collection phase above). Additionally the administration of total parenteral nutrition (TPN) was also documented as an event.

Assessment of long-term outcomes

Follow-up consultations were held at 1, 3, 6, 9 and 12 months after autologous HSCT. At these predefined follow-up visits patients were examined by both the gastroenterologist and the hematologist and laboratory testing was performed, including a full blood count with white blood cell (WBC) differentiation and C-reactive protein (CRP) level. Besides, fecal calprotectin (FCP) was determined. Additional biochemical tests and radiological examinations were performed when indicated. Endoscopic follow-up was performed at 12 months following autologous HSCT or earlier if indicated based on physician judgement. Remission was defined as absence of endoscopic signs of CD activity (i.e. SES-CD score ≤ 3).

Statistical analysis

Statistical analyses were conducted using MedCalc version 23.4.0 (survival analysis) and R software version 4.4.1 (univariate logistic regression analyses). Because of the small sample size, univariate logistic regression analyses were performed using the Firth's penalized likelihood method via the logistf package. Variables yielding a p-value of equal to or less than 0.2 in univariate analysis were subsequently included in multivariate logistic regression models. Results were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Statistical significance was defined as a two-sided p-value below 0.05.

Results

Patient demographics

Between 2011 and 2023, a total of 24 patients were eligible for autologous HSCT according to previously mentioned inclusion and exclusion criteria. All patients consented to undergo the mobilization, collection and transplantation protocol. Baseline characteristics are shown in table 1. There were 15 females (62.5%) and 9 males (37.5%). Median age at autologous HSCT was 31.0 (27.0-34.5) years with a median disease duration of 13.0 (9.8-17.3) years. All patients had small bowel disease and concomitant peri-anal disease was present in 10 patients (41.7%). Extra-intestinal manifestations were seen in 9 patients (37.5%). Seven patients (29.2%) were smoking at autologous HSCT, 5 patients (20.8%) had smoked in the past. Patients had received an average of 3.7 different MOAs (modes of action) before autologous HSCT (except for corticosteroids). All patients were previously treated with anti-TNF, while 18 patients (75%) also received vedolizumab, 6 patients (25%) ustekinumab, 2 patients (8.3%) an anti-IL23 monoclonal antibody and 5 patients (20.8%) a JAK-inhibitor prior to autologous HSCT. Sixteen patients (66.7%) had prior surgical treatment [i.e. partial (ileo)colectomy or total (procto)colectomy] for managing (complications of) CD. Four patients (16.7%) had an ostomy at the time of autologous HSCT. The median BMI at autologous HSCT was 21.9 (19.7-25.0) kg/m^2.

Mobilization and collection phase

All 24 patients underwent mobilization. Peripheral stem cell collection through cytapheresis was successful in all patients. The median CD34+ stem cell yield was 5.97 (4.68-9.01) x 10^6/kg. Neutropenia was documented in all 19 patients whereby a normal dose of Cyclophosphamide was administered. Fifteen patients (62.5%) were diagnosed with and treated for neutropenic fever, 2 patients (8.3%) were temporarily transferred to ICU because of transient hemodynamic instability. Positive blood cultures were documented in four patients (16.7%).

Transplantation phase

All 24 patients continued to the transplantation protocol. One patient started the transplantation protocol 18 months after collection but was eventually not transplanted. After rATG administration she developed neutropenic fever and respiratory failure, requiring transfer to ICU for ventilatory support and treatment of a catheter-related blood stream infection. Because of safety concerns, the conditioning regime was not completed and autologous HSCT was not performed. After recovery from neutropenia, she was successfully extubated and finally discharged from the hospital 27 days after admission. She achieved clinical, biochemical and endoscopic remission without any therapy.

The remaining 23 patients were successfully transplanted. The median number of infused CD34+ stem cells was 4.62 (4.13-5.32) x 10^6/kg. Neutropenia was documented in all patients after administration of Cyclophosphamide. Twenty-two patients (95.7%) were diagnosed with and treated for neutropenic fever, 2 patients (8.7%) were temporarily transferred to ICU because of transient hemodynamic instability. Positive blood cultures were documented in seven patients (30.4%). Temporary use of TPN was necessary in 18 patients (78.3%) because of anorexia.

Long-term outcomes

With a median follow-up of 114.6 (66.0-138.4) months all 23 patients that completed autologous HSCT are still alive. Endoscopic remission without any therapy was observed in 8 patients (34.8%). The median time to documented disease activity after autologous HSCT requiring reinitiation of advanced therapy was 7.0 (5.0-25.0) months (see figure 1). All but 2 patients (86.7%) with persistent disease activity were restarted on infliximab (only one patient experienced an allergic reaction), of which 11 patients with azathioprine (AZT) or methotrexate (MTX). One patient started ustekinumab and in one patient watchful waiting was decided because of minimal disease activity. In 7 patients (46.7%) there was persistent disease activity despite reinitiation of advanced therapy, requiring switch to another advanced therapy. Eventually surgical resections were needed in 7 patients (46.7%) with construction of an ostomy in 3 patients (20%). Univariate analysis didn't show a significant impact of various factors on the risk of persistent disease activity (see table 2).

Safety

Infectious complications occurred in 12 patients (52.2%) with varicella zoster reactivation in 6 patients (26.1%). Venous thromboembolism occurred in 1 patient (4.3%). In none of the transplanted patients we documented secondary malignancy, progressive bone marrow failure or other hematological disorders. We reported no cases of development of adrenal insufficiency after autologous HSCT, although thyroid dysfunction was present in 2 patients (8.7%). The presence of hypo- or infertility was not systematically assessed but all patients were offered fertility advice before autologous HSCT.

The not-transplanted patient was diagnosed with breast cancer and successfully treated with chemotherapy, surgery and radiotherapy 10 years after stem cell mobilization.

Table 1. — **Baseline characteristics of all included patients.**

Characteristic	All patiens (n = 24)
Gender	
Male, n (%)	9 (37.5)
Female, n (%)	15 (62.5)
Age at diagnosis in years, median (IQR)	19.0 (15.8-21.3)
Age at aHSCT in years, median (IQR)	31.0 (27.0-34.5)
Duration of disease in years, median (IQR)	13.0 (9.8-17.3)
Montreal age	
A1, n (%)	7 (29.2)
A2, n (%)	17 (70.8)
A3, n (%)	0 (0)
Montreal behavior	
B1, n (%)	2 (8.3)
B2, n (%)	5 (20.8)
B3, n (%)	17 (70.8)
pB, n (%)	14 (58.3)
Montreal location	
L1, n (%)	3 (12.5)
L2, n (%)	0 (0)
L3, n (%)	21 (87.5)
L4, n (%)	6 (25)
Extra-intestinal manifestations, n (%)	9 (37.5)
Smoking	
Active, n (%)	7 (29.2)
Stopped, n (%)	5 (20.8)
Never, n (%)	12 (50)
Prior treatment	
Anti-TNF, n (%)	24 (100)
Anti-IL12/23, n (%)	6 (25)
Anti-IL23, n (%)	2 (8.3)
Anti-integrin, n (%)	18 (75)
JAK-inhibitors, n (%)	5 (20.8)
Prior surgery, n (%)	16 (66.7)
Ileo/colostomy at aHSCT, n (%)	4 (17.4)
BMI at aHSCT in kg/m^2, median (IQR)	21.9 (19.7-25.0)

n = number of patients; IQR = interquartile range; aHSCT = autologous hematopoietic stem cell transplantation; BMI = body mass index.

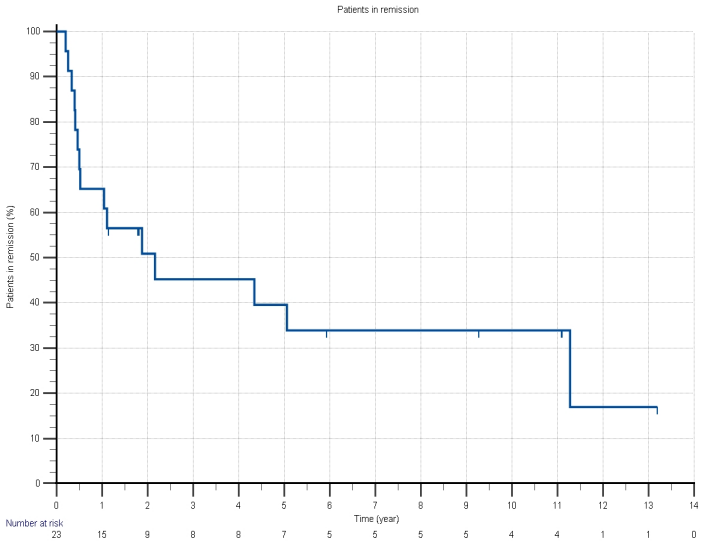

Figure 1. — Endoscopic remission-free survival.
Number at risk = number of patients at risk.

Table 2. — **Univariate analysis to identify predictors of disease persistence/recurrence.**

Characteristic	N	exp(bèta)	95% CI	p-value
Gender	15			
Male		-	-	
Female		0.88	0.00, 173	>0.9
Age at diagnosis	15	1.05	0.22, 3.64	0.9
Duration of disease	15	0.92	0.48, 2.84	0.7
Previous surgical treatment	15	1.46	0.01, 287	0.9
Montreal location	15			
L1		-	-	
L3		5.40	0.03, 1.13	0.4
Montreal behavior	15			
B1		-	-	
B2		2.33	0.01, 554	0.7
B3 or B2 + B3		7.67	0.04, 1.74	0.4
Perianal disease	15	1.46	0.01, 287	0.9
Smoking at aHSCT	15			
Never		-	-	
Active		0.43	0.00, 85.3	0.7
Stopped		0.14	0.00, 31.3	0.4
Days of neutropenia after mobilisation	15	0.82	0.36, 4.26	0.5
Days of neutropenia after aHSCT	15	0.56	0.06, 48.7	0.5
CRP at aHSCT	15	0.99	0.93, 1.11	0.7
Total days of neutropenia	15	0.85	0.48, 3.43	0.5
BMI at aHSCT	15	1.04	0.25, 3.93	>0.9

n = number of patients; CI = confidence interval; aHSCT = autologous hematopoietic stem cell transplantation; CRP = C-reactive protein; BMI = body mass index.

Discussion

This case series is one of the largest real-world cohorts reporting long-term outcomes of autologous HSCT for CD currently available. There was no mortality in this cohort. Eight patients (34.8%) were still free of CD activity at the end of the follow-up period, without any therapy. In 15 patients (65.2%) persistent disease activity was seen but nearly all patients achieved remission by re-exposure to the same CD medication that had previously failed, indicating that autologous HSCT somehow resets the immune system, enabling recycling of drugs which previously failed. Infliximab was restarted in 13 patients (86.7%), 7 patients (46.7%) needed switch to another biological. Eventually surgical resections were needed in 7 patients (46.7%).

These results are more or less in line with the ASTIC trial where 8.7% of the transplanted patients showed sustained disease remission compared to 4.5% in the control group (5). Pooled analysis of ASTIC, where all patients eventually underwent autologous HSCT (either immediately or after 1 year), showed more promising results with partial endoscopic healing in 82% of patients and complete endoscopic healing in half the patients (5,9).

Although persistent disease is seen in +/- 60% of patients after autologous HSCT, this percentage compares to success rates of newer biological therapies. These findings support the fact that CD is a multifactorial disorder with a combination of genetic susceptibility and environmental factors. Autologous HSCT succeeds in resetting the immune system with the result that therapy-refractory CD can be managed with conventional biological therapies again (10).

Our CPM and G-CSF based mobilization protocol was very effective with a collection success of 100%. The potential to mobilize hematopoietic stem cells in these refractory CD patients seems unaffected despite their history of longstanding severe systemic inflammation and treatment with multiple immunomodulatory and immunosuppressive medications in the (recent) past. This high success rate in these refractory CD patients stands in contrast to patients suffering from hematologic malignancy in which mobilization failure is reported to be 5-46%. The on average much younger patient age, the absence of bone marrow involvement and the absence of preceding exposure to chemotherapy can at least partially explain this difference (11).

Safety is an important issue with autologous HSCT as a non-curative treatment option for a non-malignant

condition. We reported no mortality and a few ICU admissions because of hemodynamic instability due to neutropenic fever. The high incidence of neutropenic fever during the mobilization and transplantation phase (respectively 62.5% and 95.7%) might indicate a higher susceptibility of these refractory CD patients to infections, possibly through a disrupted mucosal barrier function and an immunosuppressed state as a consequence of previous treatment with biological drugs. Therefore, we maintained a strict prophylactic antimicrobial treatment protocol from the start until the end of the treatment phases. Furthermore, there was a low threshold for association of broad-spectrum antibiotics after the onset of neutropenic fever. Nevertheless, no significant delayed morbidity (including cancerous complications) was reported during the follow-up period. These findings contrast with other case series reporting treatment-related mortality and morbidity due to immediate and delayed complications of infectious and non-infectious origin (5,6,9). A possible explanation for this difference is the previously mentioned infectious prophylaxis according to predefined in-hospital standard operating procedures in our center with experience in transplantation. In addition, studies have showed that center size and experience influences transplant-related and overall survival rates, independent of indication for autologous HSCT (9,12).

In conclusion, findings from our single-center cohort indicate that autologous HSCT is a safe and effective therapy for inducing remission and altering susceptibility to previously ineffective drugs in severe therapy-refractory CD. Although no major adverse events were observed in our case series, this treatment modality may be accompanied by significant morbidity and even mortality. Therefore, in agreement with the ECCO topical review on therapy-refractory IBD, autologous HSCT should be reserved for CD patients who have no benefit from surgery or experimental drugs (13).

Declarations

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