Allogeneic hematopoietic stem cell transplantation allows long-term complete remission and curability in high-risk Waldenström's macroglobulinemia. Results of a retrospective analysis of the Société Française de Greffe de Moelle et de Thérapie Cellulaire

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ABSTRACT

Background
Patients with poor-risk Waldenström's macroglobulinemia have suboptimal response and early post-treatment relapse with conventional therapies. Hence, new therapeutic approaches such as allogeneic stem cell transplantation should be evaluated in these patients.

Design and Methods
We examined the long-term outcome of allogeneic stem cell transplantation in Waldenström's macroglobulinemia by studying the records of 24 patients reported in the SFGM-TC database and one transplanted in the bone marrow unit in Hamburg.

Results
Median age at the time of transplant was 48 years (range, 24-64). The patients had previously received a median of 3 lines of therapy (range, 1-6) and 44% of them had refractory disease at time of transplant. Allogeneic stem cell transplantation after myeloablative (n=12) or reduced-intensity (n=13) conditioning yielded an overall response rate of 92% and immunofixation-negative complete remission in 50% of evaluable patients. With a median follow-up of 64 months among survivors (range, 11-149 months), 5-year overall survival and progression-free survival rates were respectively, 67% (95% CI: 46-81) and 58% (95% CI: 38-75). The 5-year estimated risk of progression was 25% (95% CI: 10-36%), with only one relapse among the 12 patients who entered complete remission, versus 5 in the 12 patients who did not. Only one of the 6 relapses occurred more than three years post-transplant.

Conclusions
Allogeneic stem cell transplantation yields a high rate of complete remissions and is potentially curative in poor-risk Waldenström's macroglobulinemia.

Key words: Waldenström's macroglobulinemia, allogeneic, transplantation.

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Introduction

Waldenström's macroglobulinemia (WM) is a rare low-grade lymphoplasmocytoid disorder. Median age at diagnosis is about 65 years. The disease usually has a long natural history, many patients surviving more than five years after initial diagnosis. Conventional therapies, including alkylating agents, anthracyclin-containing poly-chemotherapy (e.g. the CHOP regimen), nucleoside analogs and rituximab yield partial responses in 50-80% of cases. Complete remission is rare and most patients relapse after a median of 12-36 months.[1]

Poor-risk Waldenström's macroglobulinemia is defined by a suboptimal response to treatment and early post-treatment relapse. It is also possible to predict these outcomes at diagnosis and/or treatment initiation.[2] New therapeutic approaches are needed for these patients. High-dose chemotherapy followed by autologous stem cell transplantation is one option: it leads to frequent complete and lengthy remissions, although most patients ultimately relapse.[3,4] Allogeneic stem cell transplantation may improve tumor response due to graft-versus-tumor effect.[5-11] We have previously obtained encouraging results with allogeneic stem cell transplantation in a series of 10 patients.[4] Here we report longer follow-up of these 10 patients along with data on 15 additional cases.

Design and Methods

Study design and definitions

We retrospectively studied all Waldenström's macroglobulinemia patients who had undergone allogeneic stem cell transplantation and who were recorded in the French SFGM-TC database (Société Française de Greffe de Moelle et de Thérapie Cellulaire). We added one patient transplanted in the bone marrow unit in Hamburg. Waldenström's macroglobulinemia was diagnosed on the basis of lymphoplasmacytic cell proliferation and monoclonal IgM production, as recommended by the 2nd international Waldenström's macroglobulinemia workshop. To confirm the diagnosis of Waldenström's macroglobulinemia, the transplant centers were asked to provide a detailed histological report, an electrophoresis chart and, when available, tumor cell immunophenotyping results. The referring physicians were also contacted to obtain missing data. Patients and donors gave their prior informed consent to the data analysis.

Response criteria

We used the response criteria of Kimby *et al.*[12] As reported earlier, we also described patients in very good partial response, corresponding to patients who fulfilled all criteria of complete remission but with persistence of a detectable monoclonal IgM of less than 5 g/L, as described previously.[4]

Complete remission was defined by resolution of any adenopathy/organomegaly or signs of Waldenström's macroglobulinemia, and by negative immunofixation of monoclonal protein, even if bone marrow evaluation was not available. Patients with persistent detectable monoclonal IgM less than 5 g/L but who met all the other criteria for complete remission (even if bone marrow evaluation was not available) were considered to have a very good partial response. Partial response was defined as at least a 50% reduction in monoclonal IgM (with more than 5g/L of monoclonal IgM) and in tumor infiltration at all involved sites, together with the absence of new symptoms or signs of active disease. Minor response was defined by 25% or more but less than 50% reduction of serum monoclonal IgM and absence of new symptoms or signs of active disease. Stable disease was defined by a reduction of less than 25% or an increase of less than 25% in serum IgM on electrophoresis, with no progression of adenopathy/organomegaly, no cytopenia, and no signs of active disease. Progressive disease was defined by an increase of more than 25% in serum IgM on electrophoresis, progression of adenopathy/organomegaly, and the appearance of cytopenia or signs of active disease (hyperviscosity, neuropathy, symptomatic cryoglobulinemia, amyloidosis, unexplained recurrent fever, drenching night sweats or more than 10% body weight loss). Chemosensitive disease was represented by complete remission, very good partial response, partial response and minor response, and refractory disease by stable disease and progressive disease.

Statistical analysis

The following endpoints were analyzed: post-transplant response, overall survival, progression-free survival, transplant-related mortality, progression and acute or chronic graft-versus-host-disease. Overall survival and progression free survival curves were derived from Kaplan-Meier estimates, as were cumulative incidence rates of progression, transplant related mortality, and acute or chronic graft-versus-host-disease. Univariate analysis used log-rank tests for qualitative variables and univariate Cox models for continuous variables. Since no variable was found significant in univariate analysis, no multivariable regression was performed. The SAS 8.2 statistical package was used for all computations.

Results

Patients' characteristics

We analyzed 25 patients (11 females, 14 males) transplanted in 14 centers from 1995 to 2007. Twelve patients received myeloablative conditioning regimens while 13 patients received reduced-intensity conditioning regimens.

Patients' characteristics are shown in Table 1. At the time of stem cell transplantation, median age was 48 years (range 24-64): 45 years (range 24-57) in the myeloablative conditioning subgroup and 53 years (range 39-64) in the reduced-intensity conditioning subgroup. Most patients had already been heavily treated before stem cell transplantation with a median of 3 lines of therapy (range 1-6), and 80% of patients had received purine analogs. At the time of stem cell transplantation, 11 patients (44%) had refractory Waldenström's macroglobulinemia (4 stable disease and 7 progressive disease) and 14 patients (56%) had chemosensitive disease (13 partial response and one very good partial response). One patient had Waldenström's macroglobulinemia transformation into large B-cell lymphoma.

Transplant modalities and donors' characteristics

All 12 patients transplanted after myeloablative conditioning regimen received total body irradiation, associated with high-dose cyclophosphamide in 11 cases. Graft-ver-

sus-host-disease prophylaxis consisted of cyclosporine and short-course methotrexate.

The reduced-intensity conditioning regimens consisted in 7 patients of 2 Gy total body irradiation plus fludarabine, with graft-versus-host-disease prophylaxis combining cyclosporine and mycophenolate mofetil. For one of these 7 patients, who was transplanted from unrelated cord blood, high-dose cyclophosphamide was added to the previous conditioning regimen. In 4 patients, reduced-intensity conditioning regimen was fludarabine plus cyclophosphamide with graft-versus-host disease prophylaxis associating cyclosporine plus short-course methotrexate. In the 2 remaining cases, conditioning regimen consisted of high-dose melphalan and fludarabine in one patient and busulfan, fludarabine and antithymoglobulin in the second. Only 2 patients received antithymoglobulin as part of their conditioning regimen.

Transplants were unmanipulated except in case of ABO incompatibility. In the 13 reduced-intensity conditioning transplants, the hematopoietic stem cell source was peripheral blood in 11, bone marrow in one and cord blood in one. The hematopoietic stem cell source of the 12 patients transplanted after myeloablative conditioning was bone marrow. The donors were genoidentical siblings in 21 cases (12 myeloablative conditioning and 9 reduced-intensity conditioning), unrelated HLA-matched donors in 3 and unrelated cord blood in the remaining reduced-intensity conditioning transplants.

Response to transplant

Figure 1 shows the post-transplant response. Among 24 evaluable patients, the overall response rate observed at three months post-transplant was 91% with 4% of complete remission, 38% of very good partial response and 49% partial response. The responses improved with time and the physician taking care of these patients attested to

Table 1. Characteristics of patients.

Age lines (y)	Prev. Alk (nb)	Previous exposure to: Ant	NA	Rit	Other (m)	DDG	DST (3 m)	Cond. response	Resp. (m)	Best (m)	FU	Acute GVHD	Chronic GVHD	Prog (m)	Cause of death	Status at last FU
Myeloablative conditioning regimen																
43	2	+	+			67	PR	A Mel TBI	VGPR	CR (5)	134+	2	0			CR
42	2	+	+			33	PR	Cy TBI	VGPR	CR (13)	64+	2	0			CR
35	2		+	+		9	PD	Cy TBI	PR	CR (7)	107+	0	0			CR
50	2		+	+		16	PR	Cy TBI	VGPR	CR (15)	82+	1	L			CR
46	3	+	+	+		65	PR	Cy TBI	PR	CR (19)	87+	2	L			CR
24	3		+	+	platinum	11	PR	Cy TBI	PR	PR (3)	3	3	L		Infection	PR
57	2	+	+			56	PR	Cy TBI	PR	PR (3)	3	2	na		TMA	PR
48	3	+	+		irradiation	78	PR	Cy TBI	VGPR	VGPR (3)	104+	2	0	38		PD
39	4	+	+	+	splenectomy	20	SD	Cy TBI	PD	PD	18	2	E	3	Prog	PD
51	4	+	+	+	auto SCT	22	PD	Cy TBI	PD	PD	11	2	E	2	Progr	PD
42	3	+	+	+		61	PR	Cy TBI	VGPR	CR (15)	149+	2	L	140		CR
55	2	+		+		50	PD	Cy TT TBI	PR	PR (3)	11	2	L	10	TMA	PD
Reduced intensity conditioning regimen																
62	3		+	+	+ auto SCT	75	PR	F TBI ATG	VGPR	VGPR (5)	17+	0	0			VGPR
40	1	+				49	SD	F Cy	PR	PR#(7)	43+	2	0			PR
64	3	+	+	+		137	SD	F TBI Cy	PR	PR#(11)	37+	1	0			PR
56	4	+	+		+	71	VGPR	F TBI	VGPR	CR(12)	22	0	0		Infection	CR
39	2	+		+		22	PR	F TBI	CR	CR(3)	60+	0	E			CR
42	3	+		+	auto SCT	62	PR	F Cy	PR	VGPR(7)	11+	0	E			VGPR
57	4	+	+	+	+ auto SCT	151	PR	F TBI	PR	CR(10)	33+	1	E			CR
53	4	+		+	+splenectomy	52	PD	F B ATG	VGPR	CR(19)	61+	2	E			CR
41	3		+	+	+	17	SD	MEL F	NE	NE	4	4	E		GVH / infection	NE
46	5	+		+	+splenectomy, thalidomide	81	PD	F TBI	VGPR	CR (6)	72+	2	L			CR
63	6	+		+	+alemtuzumab	76	PD	F Cy	PR	PR (2)	2	2	na		Melanoma	PR
57	3	+		+	platinum	71	PR	F TBI	PR	PR#(9)	32+	2	L	19		PR
53	5	+		+	+vcr - steroids alemtuzumab	53	PD	FCy	PR	CR (12)	85	3	E			CR

T: transplantation; y: years, mo: months; DDG:: delay diagnosis to graft.IDT: time from diagnosis to T; DST: disease status before T; Cond: conditioning regimen. FU: follow-up. GVHD: Graft-versus-host disease. Resp.: response at 3 mo; # PR with improvement compared to the 3-month evaluation; Alk: alkylating agent-based chemotherapy, Ant: anthracycline-containing polychemotherapy, NA: nucleoside analog-based chemotherapy, Rit: rituximab-containing treatment; Auto SCT: Autologous stem cell transplantation. Cy: cyclophosphamide; TBI: total body irradiation, Mel: melphalan, A: cytarabine, TT: thiotepa, F: fludarabine; TMA: thrombotic microangiopathy; na: not applicable; NE: not evaluable. + alive at last follow-up. ATG: antithymoglobulin, vcr ; vincristin.

the achievement of the best response after a median time of seven months (range 1-19) with 50% (n=12) of evaluable patients finally achieving a complete response, 13% (n=3) a very good partial response and 29% (n=7) a partial response, whereas 2 presented a persistent refractory disease. Of note, one patient achieved complete remission only after preemptive donor lymphocyte infusion. Unfortunately, due to the retrospective nature of the study, no systematic evaluations of serum immunofixation were made, so the delay of achievement remains imprecise and in 2 out of the 3 patients with late very good partial response, this response was finally confirmed rather than complete remission because of missing immunofixation data.

Graft-versus-host-disease

Twenty patients developed acute graft-versus-host disease (grade I in 3 patients, grade II in 14 patients and grade III-IV in 3 patients). The cumulative incidence of grade II-IV acute graft-versus-host-disease was 71% (95% CI: 53-89). Among the 23 patients at risk, the one-year cumulative incidence rates of all grades of chronic and extensive chronic graft-versus-host-disease, respectively, were 65% (95% CI: 46-84) and 35% (95% CI: 16-54). No correlation was observed between the incidence of chronic graft-versus-host-disease and the risk of progression.

Outcome

Six of the 25 patients progressed after the graft (5 after

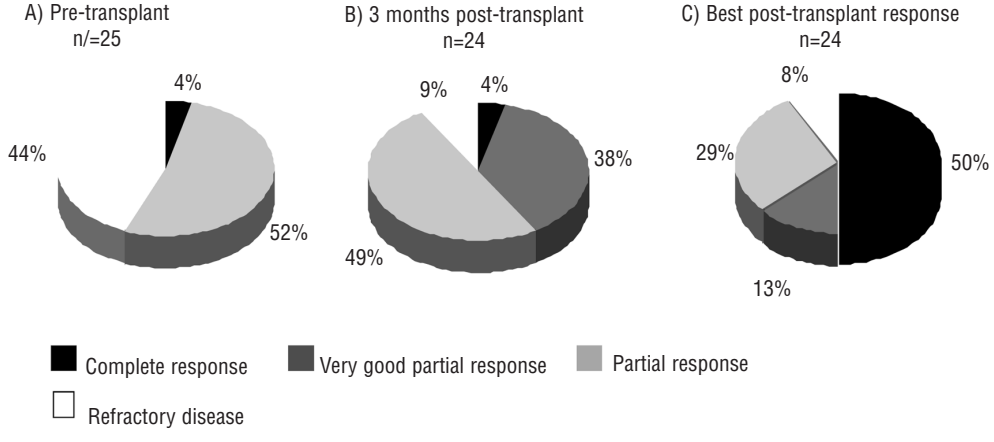

Figure 1. Response to transplant.

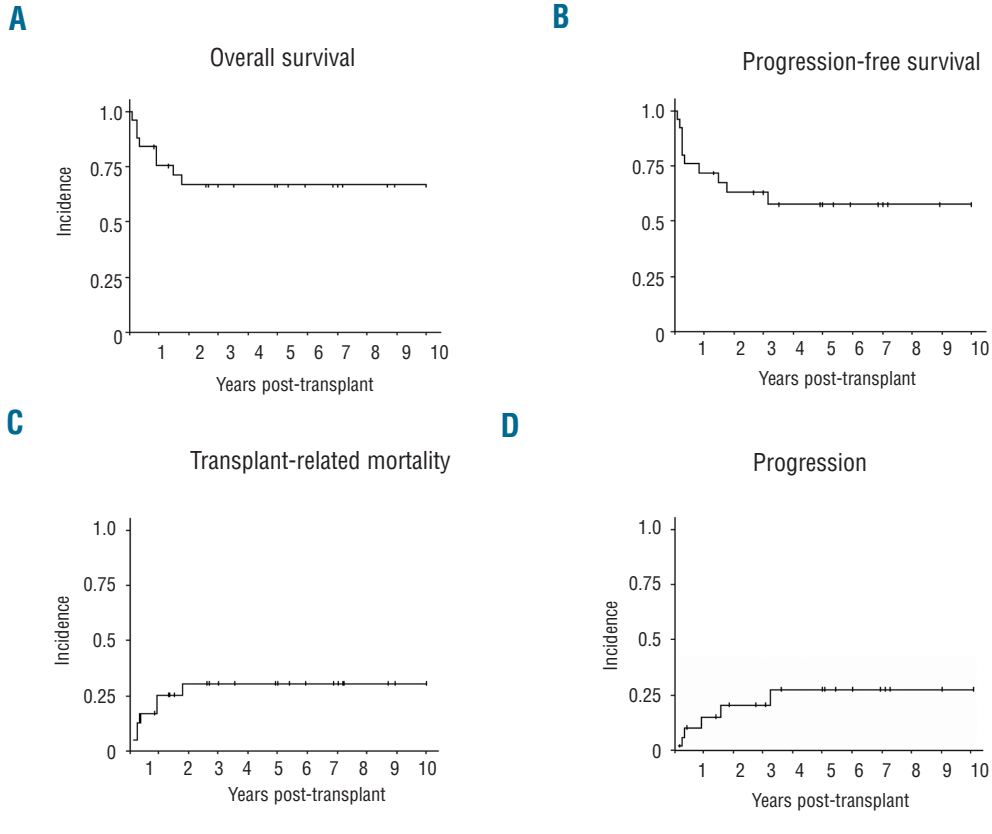

Figure 2. Post-transplant outcomes of the 25 patients.

myeloablative conditioning and one after reduced-intensity conditioning) with only one progression occurring more than three years post-graft. With a median follow-up of 63 months among surviving patients (range 11-149 months), the cumulative estimated 5-year progression rate was 25% (95% CI: 10-36) Among the 24 evaluable patients, only one of the 12 patients who entered complete remission progressed after transplant, compared to 5 of the 12 who did not enter complete remission.

Four patients received donor lymphocyte infusion: 3 for progression leading to partial response and extensive chronic graft-versus-host-disease in one patient. The remaining patient, in post-transplant partial response received early preemptive donor lymphocyte infusion (at three months) leading to complete remission and graft-versus-host-disease. This patient was alive in persistent complete remission 85 months after transplant.

The estimated 5-year overall survival rate was 67% (95% CI: 46-81) and the 5-year progression-free survival rate was 58% (95% CI: 38-75).

Six patients died from transplant-related complications (3 after myeloablative conditioning and 3 after reduced-intensity conditioning). The cause of death was melanoma (n=1) at three months post-transplant, thrombotic microangiopathy (n=2) at 3 and 11 months, graft-versus-host-disease with infection (n=1) at four months, infection (n=2) at three and 22 months. The one-year transplant-related mortality rate was 25% (95% CI: 12-44) (Figure 2).

Univariate statistical analysis

We tried to correlate selected variables to risk factors to post-transplant progression, overall survival and progression free survival.

In this small population, post-transplant outcome was not associated with any pre-transplant variables, such as age, sex, disease status, type of conditioning regimen, stem cell source, type of donor, type of previous treatment, number of lines of treatment, year of stem cell transplantation, and delay from diagnosis to the transplant. Hence mulitivariate analysis was not performed.

Discussion

The aim of this study was to confirm that long-term complete remission, and possibly cure, could be achieved with allogeneic stem cell transplantation in Waldenström's macroglobulinemia. We therefore conducted a comprehensive analysis of long-term follow-up data on all Waldenström's macroglobulinemia patients treated with allogeneic stem cell transplantation in France, as recorded in the SFGM-TC database. With assistance from the physicians in charge of the patients, the hospital files and case report forms were thoroughly crossed and double-checked to confirm the registry data. Twenty-five patients with histologically proven Waldenström's macroglobulinemia were analyzed. The overall response rate was 92%, including complete remission in 50% of evaluable patients. In this high-risk population the 5-year rate of post-graft progression was 25% with only one late relapse. Achievement of post-transplant complete response seems to be associated with low risk of progression, with relapse in this population of only 12 patients. These data led to slight monitoring of post-transplant residual disease and to propose a reduction in immunosuppressive therapy or donor lymphocyte infusion in patients with post-transplant residual disease. Conversely, in this series including both conventional and reduced intensity conditioning regimens, the limited number of patients did not allow us to demonstrate that the quality of disease control before allogeneic transplantation could influence the post-transplant complete remission rate, relapse rate and survival.

The literature on allogeneic stem cell transplantation in Waldenström's macroglobulinemia mainly comprises the series of the Seattle Consortium[6] and the IBMTR report.[10] The Seattle Consortium reported the results of reduced-intensity conditioning allogeneic stem cell transplantation in 12 patients. Despite a shorter follow-up the results are similar to ours, with a high rate of complete remission and a low incidence of progression in patients who entered complete remission. These results further support the existence of a graft-versus-lymphoma effect in Waldenström's macroglobulinemia, and the potentially curative potential of allogeneic stem cell transplantation in this setting.

Recent data show that myeloablative conditioning has no real advantage over reduced-intensity conditioning in chronic lymphocytic leukemia.[15] Most of the IBMTR registry data on Waldenström's macroglobulinemia concern myeloablative conditioning allogeneic grafts with 40% transplant related mortality which appears higher compared to 17% in the Seattle Series and 25% in the present study including transplants with both conditioning regimens, while the progression rate was similar to both the Seattle and the present studies. These results suggest that reduced-intensity conditioning may be preferable to myeloablative conditioning in Waldenström's macroglobulinemia.

The place of allogeneic stem cell transplantation in Waldenström's macroglobulinemia remains uncertain, given new treatment strategies in this setting. Recently, first-line treatment with combinations of rituximab plus either nucleoside analogs[14] or alkylating agents[1] have been reported to yield high response rates (up to 10-20% complete remission) and a median progression-free survival time of more than three years. However, patients who relapse after these combined therapies have few remaining options. We have previously reported that high-dose chemotherapy followed by autologous stem cell transplantation in patients who have relapsed after chemotherapy or immunotherapy can yield a high response rate, including cases of complete remission and long-term disease control.[4] However, this approach does not seem able to achieve complete eradication and patients eventually relapse. Moreover, the development of this procedure in Waldenström's macroglobulinemia has probably been limited by the negative impact of nucleoside analogs on stem cell collection. In our series of relapsing patients, allogeneic stem cell transplantation led to complete remission in half of them and to some cases of long-term progression-free survival compatible with cure.

Allogeneic stem cell transplantation carries a high risk of morbidity and mortality, especially in heavily pretreated patients. Of note, we reported in our series, one case of rapidly progressing solid tumor post reduced-intensity conditioning in a patient previously heavily treated with nucleoside analogs and alemtuzumab, and 2 cases of early kidney failure related to thrombotic microangiopathy after myeloablative conditioning. A

challenge would be to identify earlier in their disease young patients with high-risk Waldenström's macroglobulinemia who might benefit from allogeneic stem cell transplantation with less toxicity. Recently, a muticentric collaborative study has established a prognostic score on a large number of previously untreated symptomatic patients who required treatment. According to this International Prognostic Scoring System for Waldenström's macroglobulinemia (IPSSWM) based on age, platelet count, hemoglobin, beta2-microglobulin rates and serum monoclonal protein concentration at treatment initiation, 5-year survival of high-risk patients mostly previously treated by alkylating agents or nucleoside analogs is 36%.[2] Moreover, the impact of this prognostic score on survival has been confirmed for the patients who received rituximab-based therapy.[15] Recently, the European Bone Marrow Transplantation Leukemia Working Party defined criteria for allogeneic transplantation in chronic lymphocytic leukemia, based on cytogenetic features or on response quality.[16] Such criteria are lacking in Waldenström's macroglobulinemia, but younger patients with early relapse after front-line treatment combining alkylating agent with purine analogs or rituximab are considered as poor-risk patients and might benefit from allogeneic transplant.

In conclusion, this study shows that allogeneic stem cell transplantation can yield high rates of complete remission and long-term progression-free survival in high-risk patients with Waldenström's macroglobulinemia. Achievement of post-transplant complete remission is associated with low-risk of relapse and curability in some patients. Better identification of such high-risk patients early in the disease course could allow allogeneic stem cell transplantation to be performed earlier, potentially with better results.

Authorship and Disclosures

AG performed the study and wrote the paper. JLG analyzed the data. OT and ND designed and performed the study, included patients and wrote the paper. All other authors included patients, followed patients clinically, updated information on outcome and reviewed the manuscript critically. All authors discussed and agreed on the final version of the paper.

The authors reported no potential conflicts of interest.

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