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Asciminib as a bridge therapy prior to allogeneic hematopoietic stem cell transplantation and in post-transplant period for chronic myeloid leukemia

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Summary

Asciminib is a novel BCR::ABL1inhibitor Specifically Targeting the ABL Myristoyl Pocket (STAMP) showing effectiveness and good safety profile according to the results of a phase I and III studies in patients with Ph-positive chronic myeloid leukemia (CML) failing prior tyrosine kinase inhibitors (TKIs). Pre-transplant use of 2nd generation TKIs (nilotinib/dasatinib) does not change the risk of complications associated with allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, there are no appropriate data for the patients who received asciminib prior to transplant. In Russia, asciminib is available under the Managed Access Program (MAP) approved by Novartis. In the MAP program 68 patients with CML were enrolled. We reviewed data of 12 patients across 2 contributing centers, who underwent allo-HSCT between August 2021 and August 2022. Our aim was to evaluate the safety and effectiveness of pre- and post-transplant asciminib in allo-HSCT candidates. The median duration of asciminib before allo-HSCT was 194 days (61-377 days). 92% of patients did not develop adverse events (AEs) of any grade. Median day of engraftment was D+20 (range 18-24). The 1-year overall survival was 70%. The cumulative incidence of acute GvHD (grade 1-3 until D+100) was 18%.

Non-relapse mortality was 18% at 12 months. Eight patients (67%) are alive with median follow-up after allo-HSCT of 135 days and achieved deep molecular response. In our observation (limited with small dataset) asciminib was effective as a bridge therapy before allo-HSCT in highly pretreated patients with low rate of severe toxicity and acceptable rate of aGvHD.

Keywords

Chronic myeloid leukemia, allo-HSCT, asciminib.

Introduction

Treatment of chronic myeloid leukemia (CML) has evolved from early 2000's to the present time. Despite the excellent long-term survival for CML patients diagnosed in CP undergoing TKI treatment and a near normal life expectancy [1], allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a treatment option for the patients with CML who failed to respond to 3 and more available TKIs or being a reserved treatment option for patients who have advanced phases of CML [2]. However, the timing of the

transplant has changed to the 3rd or 4th line after failure or intolerance to second-generation TKI (2GTKI) according to current recommendations [3]. Concerns regarding the feasibility and the safety of a subsequent allo-HSCT are justified due to some well-known side effects of 2GTKIs. For instance, myelotoxicity could predispose to delayed engraftment, or liver toxicity may result into sinusoidal obstructive syndrome (SOS).

Asciminib is a novel BCR::ABL1 inhibitor that works as STAMP (Specifically Targeting the ABL Myristoyl Pocket). It has shown effectiveness and a good safety profile according to the results of a phase I and III studies in patients with Ph-positive leukemia failing prior TKIs. Asciminib is potentially active against naïve and mutated BCR::ABL1 including T315I mutation and is currently approved for patients with chronic-phase CML (CP-CML) previously treated with two or more TKIs being also available for patients with mutation T315I [4, 5].

While pre-transplant use of 2nd-generation TKIs (nilotinib/dasatinib) does not change the risk of complications associated with allo-HSCT, there are some reports on TKI therapy, in particular, with ponatinib inducing graft-versus-host disease (GvHD) [6]. There are still no similar data available for patients receiving asciminib. The Managed Access Program (MAP) ABL001A02401M was conducted to provide asciminib to patients with chronic myeloid leukemia. Three clinical centers in Russia participated in the program (RM Gorbacheva Research Institute, Pavlov University, St. Petersburg; Almazov National Medical Research Centre, St. Petersburg; National Medical Research Center for Hematology, Moscow, Russian Federation).

Therefore, our aim was to evaluate the safety and effectiveness of pre- and post-transplant asciminib in allo-HSCT candidates.

Materials and methods

Sixty eight patients with CML were enrolled in the MAP program. We reviewed clinical data of 12 patients across 2 contributing centers, who underwent allo-HSCT between August 2021 and August 2022. Inclusion Criteria were as follows:

- Adult patients in the chronic phase CML (AP and BC are acceptable in anamnesis);
- Failure of therapy with at least two TKIs in the absence of the T315I mutation;
- Failure of therapy with any TKI in the presence of the T315I mutation;
- Lack of alternative therapies and inability to participate in clinical trials with potentially effective treatment options;
- Absence of clinically significant restrictions.

Our aim was to evaluate the safety and effectiveness of pre- and post-transplant asciminib in allo-HSCT candidates. ABL1 kinase domain mutations (KDM) were analyzed by Sanger sequencing. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0. The median age of this cohort was 41 years (range 28-59) and 8(58% 8/12=67%) patients were males (Table 1). All patients had a good performance status (PS) according to Eastern Cooperative Oncology Group (ECOG 0-1) criteria. The median duration of CML before asciminib was 2.8 years (range 0.3-15).

CML status prior to asciminib administration: all patients exhibited lack (absence) of cytogenetic or molecular response to previous treatment. Six patients had complete hematological response, six patients lacked a complete hematological response (including cytopenia). Three CML patients were in the 1st chronic phase, 4 patients had a history of accelerated phase and five patients had a history of blast crisis. The median duration of asciminib before allo-HSCT was 194 days (61-377 days). Nine (75%) patients had *BCR::ABL1* mutations, and seven (58%) had *BCR:ABL1*^{t315i}. Four (33%) patients had additional chromosomal abnormalities. The majority of patients (84%) received ≥3 TKIs, 4 patients (33%) had a history of ponatinib treatment. In five (41%) patients, the initial dose of asciminib was 40 mg twice daily (BID), seven (59%) patients started with 200 mg BID.

Eleven patients treated with asciminib (92%) did not develop adverse events (AEs) of any grade. Only one patient (8%) exhibited AEs (grade 3 neutropenia, grade 4 thrombocytopenia), However, he was able to continue treatment at a reduced dose of 20 mg BID. The pre-transplant disease status was as follows: complete hematological response for 4 patients, complete cytogenetic response (CCyR) in one case. Major molecular response (MMR) and MR4 response have been documented in two and one case, respectively. Four patients did not exhibit hematological response (Fig. 1).

Results

All patients received allo-HSCT with reduced-intensity conditioning regimen. GvHD prevention with PtCyTxMMF/PtCyCsA or monoCy/monoCsA (in case of related donor and bone marrow source) was given. Allo-HSCT was performed from related donor in 8 patients who received transplants from matched related donor and haplo donor in 5 and 3 cases respectively), and in 4 patients (33%) grafted from mismatched unrelated donors (9/10, 8/10) using PBSCs as transplant source.

Toxicity profile of the conditioning regimens is depicted in Table 1. Median day of engraftment was D+20 (range 18-24). There were 1 case of primary and 1 case of secondary graft failure observed. The 1-year overall survival was 70% (Fig. 2A).

Over the post-transplant period, 4 patients (33%) continued asciminib, due to minimal residual disease (MRD), with achievement of CMR in 3 cases (25%, Table 2). One patient developed grade 1 veno-occlusive disease (VOD) which has resolved during therapy on D+10. Two patients developed liver aGvHD (grade 2), which did not require correction of the immunosuppressive therapy. Asciminib therapy was not interrupted. Two patients developed intestinal aGvHD grade 3 requiring glucocorticosteroids and ruxolitinib treatment. In these patients, Asciminib was canceled interrupted until resolution of aGvHD. The cumulative incidence of acute GvHD (grade 1-3 until D+100) was 18% (Fig. 2B). Development of aGvHD was not associated with asciminib therapy in our group.

Table 1. Baseline characteristics of the CML patients treated with asciminib

Patient №	1	2	3	4	5	6	7	8	9	10	11	12
Age, sex	47/F	34/M	57/M	59/F	31/F	42/F	52/M	35/M	41/M	28/M	30/M	33/F
Disease phase at diagnosis	CP1	CP1	CP1	CP1	CP1	CP1	CP1	CP1	CP1	AP1	CP1	AP1
History of CML progression	BC	BC	AP	CP1	AP	CP1	BC	CP1	BC	AP1	AP	BC
Previous TKI	Ima/ Dasa/ Nilo	Ima/ Dasa/ Nilo/ Pona	Ima/ Bosu/ Pona	Ima/ Rado/ Pona	Ima/ Nilo/ Bosu/ Dasa	Ima/ Nilo/ Dasa/ Bosu	Ima/ Nilo/ Dasa/ Ima	Ima/ Dasa	Ima/ Nilo/ Dasa/ Bosu	Ima/ Bosu	Ima/ Nilo/ Dasa	Ima/ Bosu/ Dasa
ABL-kinase domain mutation	F317V	T315I	T315I	T315I	T315I	none	T315I	T315I	F317L	T315I, V299L	none	none
History of ACA in Ph+ cells/ atypical type bcr-abl	none	+21, +der(22), del(11)(q23)	+Y, +8	-	-	p190	p190	p190	t(6;9;22), t(Y;5)	p190	-7, +8/ GE16	-
Disease phase before asciminib	CP2	CP2	AP	CP1	CP2	CP1	CP3	CP1	CP3	CP2	CP2	CP2
Asciminib starting dose	40 BD	200 BD	200 BD	200 BD	40 BD	40 BD	200 BD	200 BD	40 BD	200 BD	40 BD	40 BD
Disease status at HSCT	no CHR	no CHR	CHR	no CHR	CHR	no CHR	CMR	MMR	no CHR	CHR	no CHR	CHR
Donor/ Conditioning	Haplo/ RIC	MRD/ RIC	Haplo/ RIC	MRD/ RIC	MRD/ RIC	MUD m/m / RIC	MUD/ RIC	MUD/ RIC	MRD/ RIC	MRD/ RIC	MUD m/m / RIC	MUD/ RIC
Acute GvHD (Gr)	no	no	no	no	Gr 1	Gr 3	no	Gr 3	no	Gr1	Gr 3	no
Start asciminib Post-HSCT	yes	no	no	yes	yes	yes	no	no	no	yes	no	no
Response	Primary graft failure	CMR	CMR	CHR	CMR	CMR	sepsis	CMR	progression	CMR	CMR	Secondary graft failure
Mortality Status	died	alive	alive	alive	alive	alive	died	alive	died	alive	alive	ded

Notes: F, Female; M, male; CP1, chronic phase 1; CP2, 2nd chronic phase; CP3, 3rd chronic phase; AP, acceleration phase; BC, blast crisis; Ima, Imatinib; Nilo, Nilotinib; Dasa, Dasatinib; BD, twice daily; CHR, complete hematological response; MMR, major molecular response; CMR, complete molecular response; Haplo, Haploidentical donor; MRD, matched related donor; MUD, matched unrelated donor; RIC, reduced-intensity conditioning; Gr, grade.

Table 2. Responses to asciminib administered after allo-HSCT

Pts	Cause	Dose	Day	Response
1	MRD	40 mg BD	+60	CMR
2	MRD	20 mg BD	+30	impossible to assess (death)
3	MRD	40 mg BD	+30	CMR
4	MRD	40 mg BD	+60	CMR

Abbreviations: MRD, matched related donor; BD, twice daily; CMR, complete molecular response.

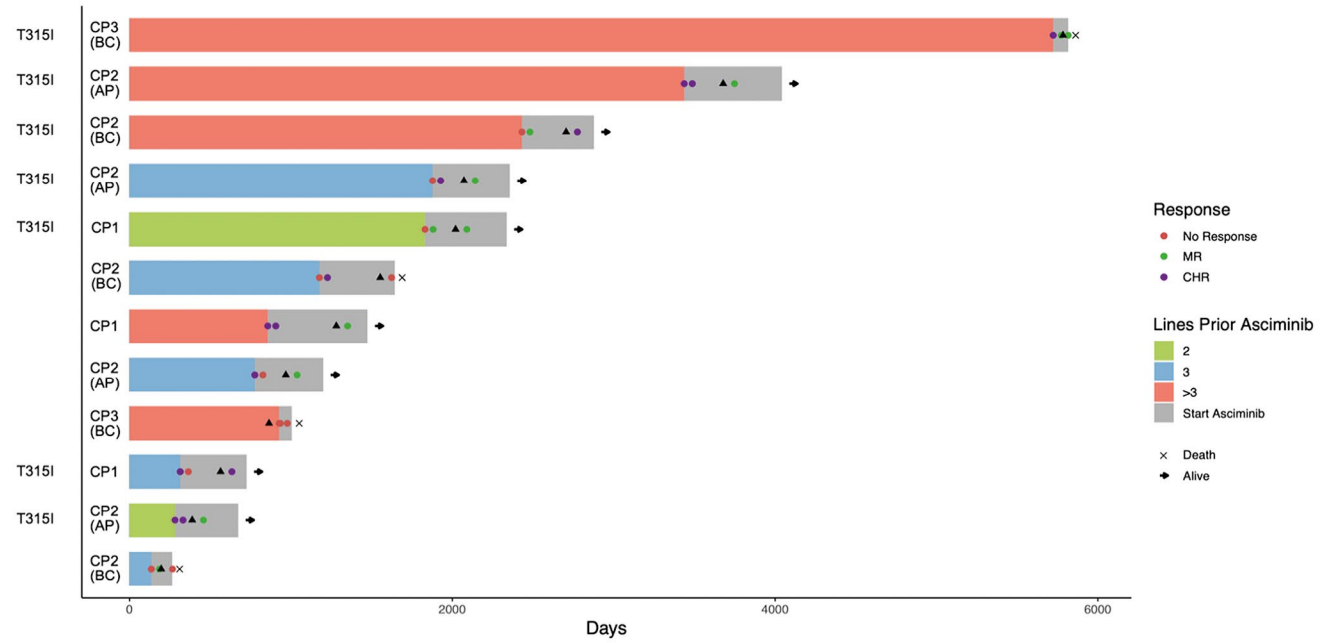

Figure 1. Summary graph of responses to Asciminib treatment in CML patients

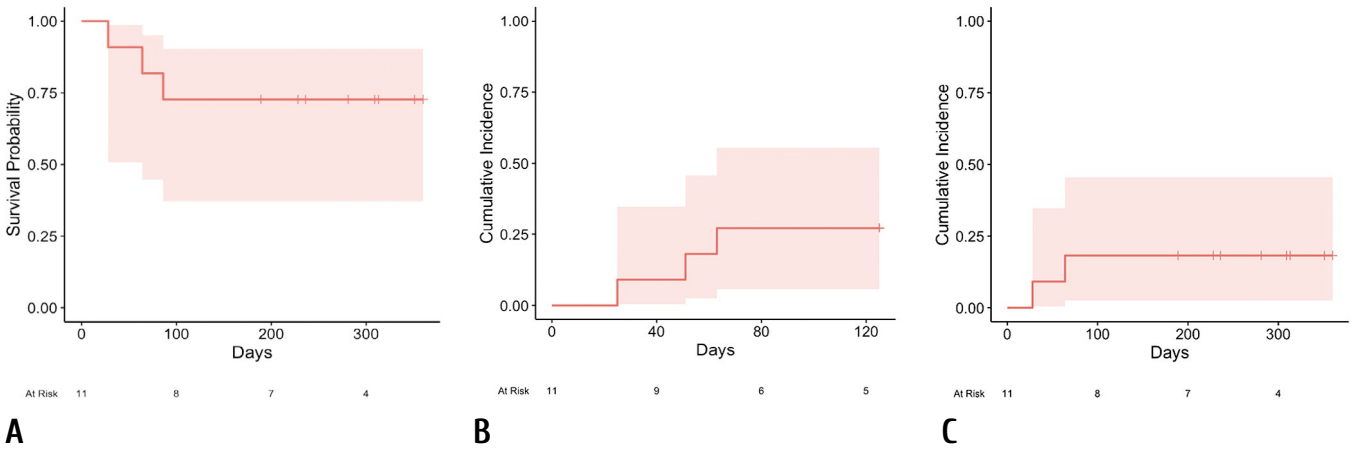

Figure 2. 1-year overall survival (A); cumulative incidence of aGvHD (B), and non-relapse mortality (C) following Asciminib treatment in CML patients

Eight patients (67%) are alive with median follow-up after allo-HSCT of 135 days. Causes of death were: sepsis, CML progression, secondary graft failure in 1, 2, 1 cases respectively. Non-relapse mortality was 18% at 12 months (Fig. 2C).

Discussion

While imatinib seems to have no adverse impact on outcomes after transplant, little is known about its effects of prior use of second-generation TKI (2GTKI). Stavroula Masouridi-Levrat et al. [7] presented the results of a prospective non-interventional study performed by EBMT in 383 CML patients previously treated with dasatinib or nilotinib undergoing allo-HSCT from 2009 to 2013. The choice of 2GTKI was as follows: 40% dasatinib, 17% nilotinib, and 43% a sequential treatment of dasatinib and nilotinib with or without bosutinib/ponatinib. No differences were found for the incidence of post-transplant complications and clinical outcomes between the different 2GTKI subgroups. This prospective study demonstrates feasibility of allo-HCT in patients previously treated with 2GTKI, with rates of post-transplant complications comparable to that among TKI-naive or imatinib-treated patients [7]. This results confirm prior observations: during the first 5 years of 2GTKI use, three retrospective studies [8-10] analyzing the outcome in a total of 43 patients who underwent allo-HCT following dasatinib or nilotinib treatment after imatinib failure provided no evidence for increased risk of graft failure or delayed engraftment, treatment-related organ toxicity, or GvHD. Y. Chalandon et al. (2023) reported that neither a number of TKIs, nor the choice of TKIs given prior to allo-HSCT for CML impacts upon survival outcome of those patients, thus also suggesting that the biology of the disease most likely determines the overall outcome [11].

TKIs also are used to treat molecular relapse after allo-HSCT and may be administered as maintenance post-HSCT in high risk patients. Fiona Fernando et al. (2023) presented that post-transplant asciminib was well tolerated and induced improvement in molecular response in heavily pre-treated cohort of patients, leading to acceptable control of disease. The majority of patients attained MMR or better quality of remission, improving their molecular response from asciminib initiation, despite previous resistance to multiple TKIs. Within this patient group, the patients with pre-transplant ponatinib resistance also achieved a deep molecular response [12].

Conclusions

In summary, asciminib showed promising results for the therapy of heavily pre-treated CML patients from the Phase 1 data and ASCEMBL study. In our observation (limited with small dataset) asciminib was effective as a bridge therapy before allo-HSCT in highly pretreated patients with low rate of severe toxicity and acceptable rate of aGvHD. It seems that in patients with advanced CML phases, asciminib is a promising drug to improve the status of the disease before allo-HSCT without an increase of aGvHD rate after allo-HSCT.

Pre-transplantation asciminib treatment does not adversely impact the post-transplant outcomes. Post-transplant asciminib induced an improved molecular response in this heavily pre-treated cohort of patients. The majority of patients attained deep molecular response. More data obtained on larger cohort is needed in order to assess its impact on long-term survival.

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Contributions

All authors reviewed and edited the manuscript and figures. All authors approved the final manuscript version.

Conflict of interest

None declared.

References

1. Hoffmann VS, Baccarani M, Hasford J, Castagnetti F, Di Raimondo F, Casado LF, et al. Treatment and outcome of 2904 CML patients from the EUTOS population-based registry. Leukemia. 2017;31(3):593-601. doi: 10.1038/leu.2016.246

2. Barrett AJ, Ito S. The role of stem cell transplantation for chronic myelogenous leukemia in the 21st century. Blood. 2015;125(21):3230-3235. doi: 10.1182/blood-2014-10-567784

3. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-884. doi: 10.1182/blood-2013-05-501569

4. Réa D, Mauro MJ, Boquimpani C, Minami Y, Lomaia E, Voloshin S, Turkina A, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021;138(21):2031-2041. doi: 10.1182/blood.2020009984

5. Hughes TP, Mauro MJ, Cortes JE, Minami H, Rea D, DeAngelo DJ, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. N Engl J Med. 2019; 381(24):2315-2326. doi: 10.1056/NEJMoa1902328

6. Petrungaro A, Gentile M, Mazzone C, Greco R, Uccello G, Recchia A, et al. Ponatinib-induced graft-versus-host disease/graft-versus-leukemia effect in a patient with philadelphia-positive acute lymphoblastic leukemia without the T315I mutation relapsing after allogeneic transplant. Chemotherapy. 2017; 62(6): 353-356. doi: 10.1159/000477714

7. Masouridi-Levrat S, Olavarria E, Iacobelli S, Aljurf M, Morozova E, Niittyvuopio R, et al. Outcomes and toxicity of allogeneic hematopoietic cell transplantation in chronic myeloid leukemia patients previously treated with second-generation tyrosine kinase inhibitors: a prospective non-interventional study from the Chronic Malignancy Working Party of the EBMT. Bone Marrow Transplant. 2022; 57(1):23-30. doi: 10.1038/s41409-021-01472-x

8. Jabbour E, Cortes J, Kantarjian H, Giralt S, Andersson BS, Giles F, et al. Novel tyrosine kinase inhibitor therapy before allogeneic stem cell transplantation in patients with chronic myeloid leukemia: no evidence for increased transplant-related toxicity. Cancer. 2007;110(2):340-344. doi: 10.1002/cncr.22778

9. Shimoni A, Leiba M, Schleuning M, Martineau G, Renaud M, Koren-Michowitz M, et al. Prior treatment with the tyrosine kinase inhibitors dasatinib and nilotinib allows stem cell transplantation (SCT) in a less advanced disease phase and does not increase SCT in patients with chronic myelogenous leukemia and Philadelphia-positive acute lymphoblastic leukemia. Leukemia. 2009; 23(1):190-194. doi: 10.1038/leu.2008.160

10. Breccia M, Palandri F, Iori AP, Colaci E, Latagliata R, Castagnetti F, et al. Second-generation tyrosine kinase inhibitors before allogeneic stem cell transplantation in patients with chronic myeloid leukemia resistant to imatinib. Leuk Res. 2010; 34(2):143-147. doi: 10.1016/j.leukres.2009.04.036

11. Chalandon Y, Sbianchi G, Gras L, Koster L, Apperley J, Byrne J, et al. Allogeneic hematopoietic cell transplantation in patients with chronic phase chronic myeloid leukemia in the era of third generation tyrosine kinase inhibitors: A retrospective study by the chronic malignancies working party of the EBMT. Am J Hematol. 2023; 98(1):112-121. doi: 10.1002/ajh.26764

12. Fernando F, Innes AJ, Claudiani S, Pryce A, Hayden C, Byrne J, et al. The outcome of post-transplant asciminib in patients with chronic myeloid leukaemia. Bone Marrow Transplant. 2023; 58(7):826-828. doi: 10.1038/s41409-023-01975-9

Асциминиб в качестве «бридж»-терапии перед аллогенной трансплантацией гемопоэтических стволовых клеток при хроническом миелоидном лейкозе

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Резюме

Асциминиб является новым ингибитором BCR::ABL, который действует посредством STAMP(Specifically Targeting the ABL Myristoyl Pocket), блокируя BCR::ABL1 киназу за счет взаимодействия с миристоиловым карманом. Препарат продемонстрировал эффективность и благоприятный профиль безопасности, согласно результатам исследования I и III фазы у пациентов с Ph+ ХМЛ, резистентным к предыдущей терапии ИТК. В то время как предтрансплантационное использование ИТК 2-го поколения (нилотиниб/дазатиниб) не изменяет риски, связанные с аллогенной трансплантацией гемопоэтических стволовых клеток (алло-ТГСК), пока нет подобных данных о пациентах, получающих перед алло-ТГСК асциминиб. В России асциминиб был доступен в рамках Программы управляемого доступа (МАР), одобренной Novartis. В программу МАР было включено 68 пациентов с ХМЛ. Мы проанализировали данные 12 пациентов из 2-х трансплантационных центров, которым была проведена алло-ТГСК в период с августа 2021 г. по август 2022 г. Наша цель заключалась в том, чтобы оценить безопасность и эффективность асциминиба до и после алло-ТГСК. Медиана продолжительности лечения асциминибом до алло-ТГСК составила 194 дня (61-377 дней). У 92% пациентов не развилось нежелательных явлений (НЯ) любой степени тяжести. Медиана приживления составила 20 дней (диапазон 18-24). Общая выживаемость в течение 1 года составила 70%. Кумулятивная частота острой РТПХ (от 1 до 3 степени до D+100) составила 18%. В нашей группе развитие оРТПХ не было обусловлено приемом асциминиба. Безрецидивная смертность составила 18% через 12 месяцев. Восемь пациентов (67%) живы, средняя продолжительность наблюдения после алло-ТГСК составила 135 дней. У всех пациентов достигнут глубокий молекулярный ответ. В нашем наблюдении (ограниченном небольшим набором данных) асциминиб был эффективен в качестве bridge-терапии перед алло-ТГСК у пациентов с несколькими линиями ИТК. Предтрансплантационное лечение асциминибом не оказывало негативного влияния на результаты трансплантации. Необходимо больше данных, полученных по более крупной когорте, чтобы оценить влияние препарата на долгосрочную выживаемость.

Ключевые слова

Хронический миелоидный лейкоз, алло-ТГСК, асциминиб.