The impact of pretransplant use of tyrosine kinase inhibitors on allogeneic stem cell transplantation in patients with chronic myeloid leukemia - A single-institution retrospective study

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Abstract

Second- and third-generation (2/3G) tyrosine kinase inhibitors (TKIs) possess excellent treatment effects on chronic myeloid leukemia (CML), and at least one 2/3G TKI is mostly incorporated into the first treatment of CML in all phases. However, the impact of 2/3G TKIs on subsequent allogeneic stem cell transplantation (allo-SCT) remains to be elucidated. We retrospectively evaluated how pretransplant therapy with TKIs affects the outcome of allo-SCT for CML using the clinical data of thirty-two patients with CML transplanted between 2001 and 2020 at our institution. Except for 11 patients who remained in the chronic phase (CP) until the time of allo-SCT, 10 patients were initially diagnosed with accelerated or blastic phase (AP/BP), and 11 patients progressed to AP/BP during the treatment for CP. With subsequent use of 2/3G TKI or imatinib (IM), 10 and 4 patients returned to the second CP at the time of allo-SCT, respectively. In univariate analysis, pretransplant use of 2/3 GTKI was significantly associated with higher 5-year overall survival (91.7%) and relapse-free survival (75.0%) than the use of IM (37.5% and 12.5%, respectively) in patients presenting with or progressing to AP/BP before allo-SCT. Our results suggest that pretransplant use of 2/3G TKI improves the outcome of allo-SCT in CML patients who present with AP/BP at diagnosis or progress to the advanced phase thereafter.

Introduction

Allogeneic stem cell transplantation (allo-SCT) has been actively performed as a curative treatment for chronic myeloid leukemia (CML) until the introduction of imatinib [1]. Based on data from the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT), the number of allo-SCTs for CML continued to decline to 96 in 2003 and 54 in 2007 [2], and the number remained unchanged thereafter, suggesting that allo-SCT remains an important treatment option for CML, especially in advanced phases. According to the European LeukemiaNet (ELN) recommendations, allo-SCT should be considered for patients resistant to or intolerant to two or more TKIs and for patients presenting as or progressing to accelerated/blastic phase (AP/BP) [3].

Second- and third-generation (2/3G) TKIs possess a higher treatment response than imatinib not only to newly diagnosed CML patients in the chronic phase (CP) [4–5] but also to patients with imatinib resistance/intolerance [6–8] and advanced-phase CML [9–11]. Currently, most CML patients undergoing allo-SCT receive at least one 2/3G TKI. Several studies reported the effect of pretransplant use of TKI on the outcome of allo-SCT [12–14]; however, most of the studies focused on the first generation of TKI or imatinib only, and few studies assessed the impact of 2/3G TKIs on the transplantoutcomes [15–17]. To clarify this issue, we retrospectively analyzed the data on CML patients undergoing allo-SCT at our institute, focusing on the impact of pretransplant use of TKIs on transplant outcomes.

Materials And Methods

Patients and definitions

This retrospective study analyzed the clinical records of patients with CML at Keio University Hospital (Tokyo, Japan). Thirty-two patients who received the first allo-SCT at our institute from 2001 to 2020 were included in this study. The patients were divided into CP and AP/BP according to disease phase at diagnosis [18]. We also added another category (progressing phase) by the trajectory changes of disease phase between diagnosis and transplant. Patients transplanted in the second CP (CP2) were either diagnosed in the accelerated phase (AP) or blast phase (BP) or diagnosed initially as CP but progressed to more advanced disease and returned to CP at the time of allo-SCT [16, 19], and progressing phase CML was defined as CP2, AP or BP at the time of SCT. We also divided patients into three subgroups based on TKI treatment before allo-SCT: the non-TKI group included patients who did not receive any TKI. The IM group represented patients who received only imatinib (IM), and the 2/3G TKI group represented patients who received at least one 2G and/or 3G TKI. This study was approved by the Ethics Committee of Keio University School of Medicine.

Responses were defined using ELN criteria [3]. Transplantation-related risk was assessed using the European Group for Blood and Marrow Transplantation (EBMT) score [20]. Relapse was defined as progression to AP/BP, hematologic relapse, cytogenetic relapse, or molecular relapse. Molecular relapse was defined as positivity of BCR-ABL transcripts in quantitative reverse transcription PCR (RT-PCR) with a ratio of BCR-ABL to ABL of 10^{-5} or more in at least two measurements. Acute and chronic graft versus host disease (GVHD) were graded according to clinical consensus criteria [21–22]. Measurement of BCR-ABL was performed at our institute for clinical genetics. The International Scale (IS) was consecutively introduced after 2015. In terms of conditioning regimens in allo-SCT, myeloablative conditioning and reduced-intensity conditioning were defined according to the definition of the Center for International Blood and Marrow Transplant Research [23].

Statistical analysis

The differences between the groups were compared using Fisher's exact test or Mann-Whitney's U-test as appropriate. The probabilities of overall survival (OS) and relapse-free survival (RFS) were calculated by the Kaplan-Meier method. Estimates of nonrelapse mortality (NRM) and relapse/progression were calculated using the cumulative incidence rate (CIR) to accommodate competing risks and were compared by Gray's test. The following variables were considered in univariate analysis: age at SCT, sex, donor-recipient sex matching, duration from diagnosis to transplant, disease status at diagnosis, SCT, use of TKI before transplant, types and numbers of TKIs used before transplant, type of donor, use of TKI after transplant, and EBMT score. *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed using EZR, which is a graphical user interface for R [24].

Results

Patients and pretransplant treatment characteristics

A total of 32 patients were included in the analysis. Of those, 22 patients had CP, 10 patients had AP/BP at diagnosis, and 21 patients were in the progressing phase. Patient and transplant characteristics according to disease status are shown in Table 1. In the CP group, seven patients received IM only, 6 patients received not only IM but also 2G TKI, and no patients received 3G TKI. In the AP/BP group, 2 patients received IM only, 4 patients received 2G TKI, and 4 patients received 3G TKI. In the progression phase group, 8 patients received IM only, 8 patients received 2G TKI, and 4 patients received 3G TKI.

Year of SCT, disease status at SCT, numbers of TKIs used before transplant, and EBMT risk score were significantly different in each treatment group in the CP group; there were more patients in the progressing phase (CP2/AP/BP) at transplant in the IM and 2/3G TKI groups than in the non-TKI group in the CP group. The year of SCT, disease status at SCT, and number of TKIs used before transplant were significantly different in each treatment group in the AP/BP group; there were more patients in CP2 at transplant in the 2/3G TKI group than in the IM group in the AP/BP group. The duration from diagnosis to SCT was shorter in the 2/3G TKI group than in the non-TKI and IM groups in the progression phase group. The transitions of disease status from diagnosis to transplant according to pre-SCT treatments are shown in Fig. 1. In CP patients, one out of nine patients progressed to AP at transplant in the non-TKI group. In addition, 6 out of 7 patients progressed to AP/BP, but 4 patients returned to CP2 at transplant in IM group, whereas 4 out of 6 patients progressed to AP/BP, but 2 patients returned to CP2 at transplant in the 2/3G TKI group. In AP/BP patients, no patients achieved CP2 at transplant in the IM group, whereas all the patients achieved CP2 in the 2/3G TKI group.

Patient characteristics and their treatment in the progressing phase group

Patient characteristics in the progressing phase group are shown in Table 2. In the non-TKI group, one patient progressed from CP to AP during interferon (IFN) treatment and survived after allo-SCT without relapse. In the IM group, 4 out of 8 patients achieved CP2 at transplant, 5 patients relapsed, and 3 and 2 patients died because of relapse and NRM; six patients progressed from CP to AP/BP during IFN treatment, but 4 patients returned to CP2 at transplant after receiving IM with chemotherapy (CHT). Two AP/BP patients at diagnosis could not achieve CP2 at transplant with the pretransplant use of IM. In the 2/3G TKI group, 10 out of 12 patients achieved CP2 at transplant, 2 patients relapsed, and only one patient died because of NRM; four patients progressed from CP to AP/BP during the treatment of IM, but 2 patients returned to CP2 at transplant after receiving 2/3G TKI with and without CHT. All eight AP/BP patients at diagnosis achieved CP2 at transplant with the pretransplant use of 2/3G TKI with and without CHT.

The types of BP crisis were myeloid (n = 2) and lymphoid (n = 3) in the IM group and myeloid (n = 1), lymphoid (n = 8), and biphenotypic (n = 1) in the 2/3G TKI group. HDAraC was administered as pretransplant CHT in case of myeloid crisis, and the Japan Adult Leukemia Study Group Ph + ALL induction regimen, Cancer and Leukemia Group B study 9111 induction regimen, adriamycin with vincristine and prednisolone (AdVP), VP, or Hyper-CVAD was administered in case of lymphoid or biphenotypic crisis except two patients.

Transplant outcomes

All patients achieved engraftment. Fourteen of 22 patients who had CP at diagnosis, 8 of 10 patients who had AP/BP at diagnosis, and 15 out of 21 patients in the progressing phase group were alive at the time of the last follow-up. The cumulative incidences of acute (> Grade I) GVHD at day 100 were 68.2% (95% CI, 43.3–83.9%) in the CP group, 30.0% (95% CI, 6.3–59.3%) in the AP/BP group, and 47.6% (95% CI, 25.0-67.2%) in the progressing phase group. The cumulative incidences of chronic GVHD at 1 year were 62.2% (95% CI, 37.1–79.7%) in the CP group, 52.0% (95% CI, 16.0-79.2%) in the AP/BP group, and 43.3% (95% CI, 21.3–63.6%) in the progressing phase group. The median follow-up periods for survivors were 228 months (range, 50–251) in the CP group, 63 months (range, 35–116) in the AP/BP group, and 97 months (range, 35–243) in the progressing phase group. The causes of NRM were bacterial pneumonia (n = 2), chronic GVHD (n = 2), acute GVHD (n = 3), and cytomegalovirus colitis (n = 1) in the CP group and bacterial pneumonia (n = 1), chronic GVHD (n = 1), and cytomegalovirus colitis (n = 1) in the progressing phase group. No NRM was observed in the AP/BP group. The cumulative incidences of NRM at 5 years were 34.7% (95% CI, 14.8–55.6%) in the CP group, 0% in the AP/BP group, and 14.9% (95% CI, 3.5–33.9%) in the progressing phase group. The cumulative incidences of disease relapse/progression at 5 years were 11.5% (95% CI, 1.7–31.7%) in the CP group, 30.0% (95% CI, 6.2–59.3%) in the AP/BP group, and 22.0% (95% CI, 6.4–43.4%) in the progressing phase group. The 5-year OS rates were 63.6% (95% CI, 40.3–79.9%) in the CP group, 80.0% (95% CI, 40.9–94.6%) in the AP/BP group, and 71.4% (95% CI, 47.2–86.0%) in the progressing phase group. The 5-year RFS rates were 40.9% (95% CI, 20.9–60.1%) in the CP group, 70.0% (95% CI, 32.9–89.2%) in the AP/BP group, and 52.4% (95% CI, 29.7–70.9%) in the progressing phase group.

Five patients received posttransplant TKIs, and all the patients were in the progressing phase group. The details of posttransplant treatment with TKIs are shown in Table 2. Posttransplant TKIs were used in two patients for progression to BP and in one patient for molecular relapse in the CP group and in two patients for molecular relapse in the AP/BP group.

Factors affecting transplant outcomes

In the CP group, age at SCT (< 40 vs ≥ 40) was associated with RFS in univariate analysis (Supplementary Table 1). No factors were associated with OS, NRM or CIR in the CP group.

In the progressing phase group, the types of TKIs used before transplant (IM vs 2/3G TKI) and the numbers of TKIs used before transplant (1 vs ≥ 2) were the factors associated with OS and RFS in univariate analysis (Table 3). In addition, the 5-year RFS and NRM were considerably higher and lower, respectively, in patients with a shorter duration from diagnosis to transplant (< 12 vs ≥ 12), although the difference was not statistically significant (P = 0.06 and P = 0.10). Additionally, disease status at transplant (AP/BP vs CP) was considerably associated with the 5-year OS, although the association was not statistically significant (P = 0.07).

Impact of pretransplant TKIs on transplant outcome

In the CP group, the use of TKI before transplant (non-TKI vs TKI) and the types of TKIs used before transplant (non-TKI vs IM vs 2/3G TKI) were not associated with OS, RFS, NRM, or CIR (Supplementary Table 1). In the AP/BP group, we could not perform univariate analysis because there were only 2 and 8 patients in the IM and 2/3G TKI groups, respectively. However, 2 out of 2 patients in the IM group could not achieve CP2 at transplant and relapsed as progression to BP and died. On the other hand, 8 out of 8 patients in the 2/3G TKI group achieved CP2 at transplant, and one patient relapsed as molecular relapse but survived with the posttransplant TKI (Table 2). The median OS was 32 months (range, 29–35) in the IM group and 63 months (range, 35–116) in the 2/3G TKI group. The 5-year OS and RFS were 100.0% and 87.5% (95% CI, 38.7–98.1%), respectively, in the 2/3G TKI group.

In the progressing phase group, we could not perform univariate analysis for the non-TKI group because there was only one patient. The 5-year OS and RFS were significantly higher in the 2/3G TKI group (5-year OS; 91.7% (95% CI, 53.9–98.8%), 5-year RFS; 75.0% (95% CI, 40.8–91.2%)) than in the IM group (5-year OS; 37.5% (95% CI, 8.7–67.4%), 5-year RFS; 12.5% (95% CI, 7.0-42.3%) (Fig. 2a-b) in univariate analysis. In addition, the 5-year CIR was considerably lower in the 2/3G TKI group (8.3% (95% CI, 0.4–32.4%)) than in the IM group (51.4% (95% CI, 5.8–85.6%)) (Fig. 2c), although the difference was not statistically significant (P = 0.09).

Discussion

The results of this study indicate that pretransplant use of 2/3G TKI improves survival of CML patients in progressing phase group; patients who presented as AP/BP at diagnosis, and presented as CP but progressed to AP/BP by making it possible for those patients to achieve CP2 at transplant and receive allo-SCT in better settings, leading to superior OS and RFS and a lower incidence of relapse.

Since the introduction of TKIs as an initial treatment, the life expectancy of patients with CML-CP has become comparable to that of the general population [25]. However, allo-SCT remains an important treatment option for patients resistant to or intolerant to two or more TKIs and those who present with or progress to AP/BP [3]. There have been some studies evaluating the effect of pretransplant use of TKIs on the outcome of allo-SCT. Previous studies including a large number of patients showed that pretransplant use of imatinib did not adversely affect the transplantation outcome [12–14]. The 2/3G TKIs have shown good therapeutic response to CML with newly diagnosed [4–5] and imatinib-resistant/intolerant CML [6–8]. Thus, most CML patients undergoing allo-SCT receive at least one 2/3G TKI before allo-SCT. In CML-CP patients, the use of three TKIs before transplantation was shown to be a significant adverse factor for prognosis [26].

Adverse vascular events (VAEs) are one of the serious problems in patients receiving 2/3G TKI, such as pulmonary hypertension in dasatinib treatment [27], peripheral, cerebral, and coronary artery diseases in nilotinib treatment [28], and venous and arterial occlusive diseases in ponatinib treatment [29]. In addition, veno-occlusive disease (VOD) is one of the serious complications after allo-SCT in which hepatic sinusoidal vessels are damaged and obstruction of the blood flow subsequently occurs [30].

Thus, it is crucial to investigate whether pretransplant use of TKIs increases the frequency of vascular events, including VOD. Some small-scale studies evaluated the effect of pretransplant 2G TKI, and those studies suggested that the use of 2G TKI before allo-SCT did not increase transplant-related toxicity [15–17]. However, there are few large-scale studies evaluating the effect of 2/3G TKIs on the outcome of allo-SCT for CML [31–32]. Therefore, there are still insufficient data to clarify the impact of TKIs on the outcome of allo-SCT.

Recently, two large-scale studies with long-term follow-up on allo-SCT in CML evaluated the effect of pretransplant use of TKIs on transplantation outcomes [31–32]. The Turkish group retrospectively evaluated 193 CML patients receiving allo-SCT between 1989 and 2012 [31]. The 5-year OS and progression-free survival (PFS) were approximately 50% and 40%, respectively. In univariate analysis, advanced disease status at allo-SCT, not achieving hematological CR at 3 months after allo-SCT, and male recipient were associated with shorter PFS and inferior OS. The Swedish CML registry retrospectively evaluated 118 CML patients receiving allo-SCT between 2002 and 2017 [32]. The 5-year OS was 36.9–96.2% depending on the disease status at allo-SCT. The only risk factor associated with death was CP > 1 at the time of allo-SCT. In both studies, overall survival was dependent on the disease phase at allo-SCT.

Our results showed that the 5-year OS and RFS were dependent on the types of TKIs used before transplant (IM vs 2/3G TKI) and numbers of TKIs used before transplant (1 vs ≥ 2) in the progression phase group. Our results further suggested that the 5-year CIR might be dependent on the types of TKIs used before transplant (IM vs 2/3G TKI) and numbers of TKIs used before transplant (1 vs ≥ 2) in the progression phase (P = 0.09). In each group, non-TKI, IM, and 2/3G TKI subgroup patients matched with patients who received 0, 1, and ≥ 2 TKIs before transplant, respectively. Therefore, these factors represent the same clinical situation. In addition, our results also suggested that the 5-year OS might be dependent on disease status at transplant (AP/BP vs CP2) (P = 0.07), which was consistent with those of the Turkish group, Swedish CML registry studies, and the conventional EBMT scoring system [20]. However, there were some differences between our study, Turkish group, and Swedish CML registry studies, such as the percentage of type of related donor (25% vs. 96% vs. 27%) and the rate of myeloablative conditioning regimen (100% vs. 83% vs. 59%).

The limitations of our study were its retrospective nature. The clinical practice of allo-SCT may have changed, and it might lead to the heterogeneity of patient/donor and disease demographics, transplant procedures, and supportive care, which might in turn affect the treatment outcome of allo-SCT.

In conclusion, our results suggest that pretransplant use of 2/3G TKIs improves outcome in CML patients who present as or progress to AP/BP by enabling those patients to achieve CP2 at transplant and receive allo-SCT in better settings without increasing the frequency of nonrelapse mortality. An accumulation of more cases is necessary to evaluate the value of pretransplant use of 2/3 TKIs for CML.

Declarations

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Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interests

The authors declare that they have no conflicts of interest.

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The authors did not receive support from any organization for the submitted work.

Author contributions

SF conceived the idea of the study, collected data and drafted the original manuscript. MS, HK, JK, YK, KY, KS, MO, RA, TK, TS, TM, and KK contributed to the interpretation of the results. SO supervised the conduct of this study. All authors reviewed the manuscript draft and revised it critically on intellectual content. All authors approved the final version of the manuscript to be published.

Ethical approval

This study was approved by the Ethics Committee of Keio University School of Medicine.

Informed consent

Informed consent was obtained in the form of opt-out on the website. Those who rejected were excluded.

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Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

Fig. 1

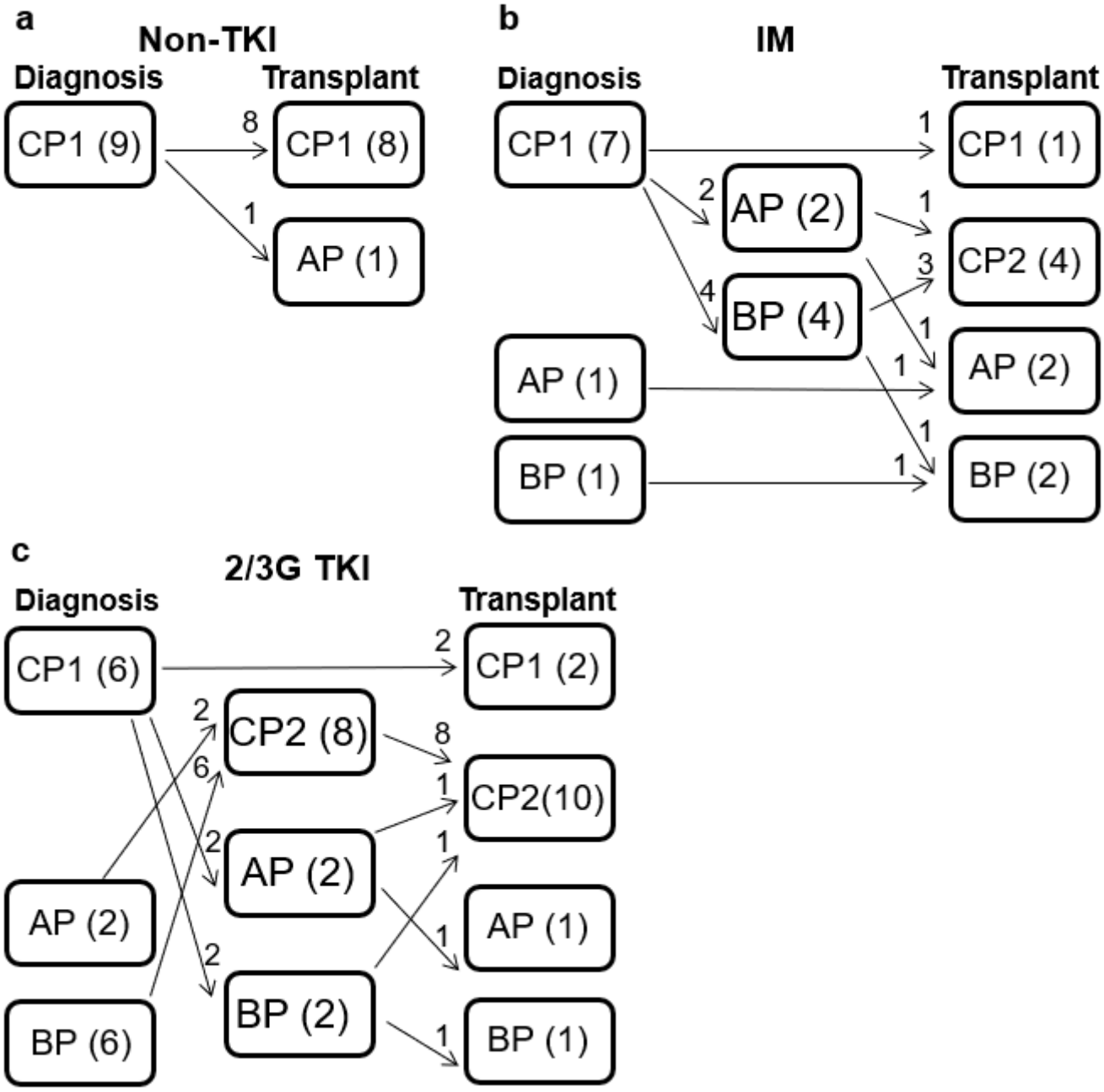

Figure 1

Transitions of disease status from diagnosis to transplant

Disease status from diagnosis to transplant for the non-TKI group (a), IM group (b), and 2/3G TKI group (c). The number of patients in each state is indicated in parentheses, and the number of patients representing the transition of disease status is indicated near above the arrow.

Fig. 2

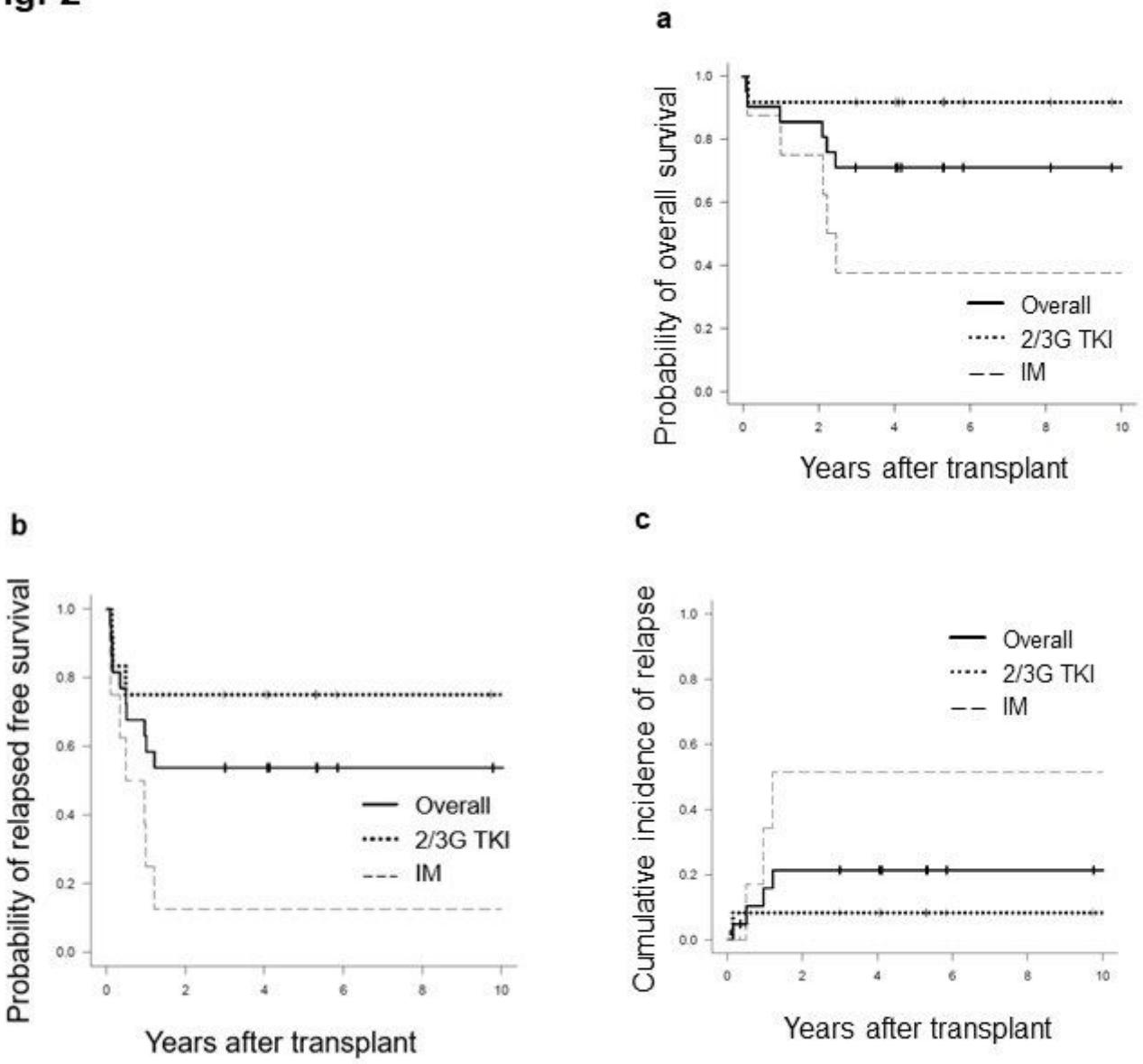

Figure 2

Kaplan-Meier analyses for overall survival (a), progression-free survival (b), and cumulative incidence of relapse (c) in progressing-phase patients

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.xlsx

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx