Prognostic significance of SET-NUP214 fusion gene in acute leukemia after allogeneic hematopoietic stem cell transplantation

Meng-Ge Gao, MSa, Yan Hong, MDa, Ya-Zhen Qin, MDa, Ying-Jun Chang, MDa,d, Yu Wang, MDa,d, Xiao-Hui Zhang, MD,a,d, Lan-Ping Xu, MD,a,d, Xiao-Jun Huang, MD,b,c,d, Xiao-Su Zhao, MD, PhD,a,c,d,*

Abstract

The SET nuclear proto-oncogene (SET)-nucleoporin (NUP) 214 fusion gene (SET-NUP214) is a rare leukemia fusion gene. Due to the limited number of samples with SET-NUP214 fusion gene in previous studies, the significance of SET-NUP214 for measurable residual disease (MRD) monitoring in patients with acute leukemia (AL) is still unclear. Our study aimed to observe the dynamic changes in SET-NUP214 expression before and after allogeneic hematopoietic stem cell transplantation (allo-HSCT), and analyzed whether SET-NUP214 could be used to evaluate MRD status. Our study included 24 AL patients who were newly diagnosed with SET-NUP214 fusion gene and they all received allo-HSCT. Their MRD was evaluated by monitoring SET-NUP214 fusion gene and leukemia-associated immunophenotype (LAIP). The median follow-up time was 501 days (56–2208 days). Of the enrolled patients, 6 (25%) patients died, including 3 (12.5%) patients died of leukemia relapse. Total 5 (20.8%) patients experienced hematological relapse at a median of 225 days (56–1057 days) post-transplantation. The SET-NUP214 median expression level at diagnosis was 405.1% (14.6%–1482.4%). SET-NUP214 gene expression generally became positive prior to flow cytometry results. In addition, the Kaplan-Meier survival curves analysis showed that those who had SET-NUP214 positive (SET-NUP214+) post-transplantation had a higher cumulative incidence of leukemia relapse (CIR) of 43.7 ± 18.8% (P < .05). However, there was no significant difference between SET-NUP214 positive and SET-NUP214 negative patients with regard to their 2-year overall survival (OS) (82.5 ± 11.3 vs 64.6 ± 17.5%, respectively, P = .271). ROC curve analysis turned out that the area under the ROC curve (AUC) was 0.916 (95% CI: 0.784–1.0; P = .005). In conclusion, SET-NUP214 fusion gene determined by real-time quantitative reverse transcriptase polymerase chain reaction (RQ-PCR) could be used to evaluate MRD status after allo-HSCT. Patients with positive SET-NUP214 expression after transplantation will have a poor prognosis.

Abbreviations: AL = acute leukemia, allo-HSCT = allogeneic hematopoietic stem cell transplantation, CIR = cumulative incidence of leukemia relapse, LAIP = leukemia-associated immunophenotype, MRD = measurable residual disease, OS = overall survival, RQ-PCR = real-time quantitative reverse transcriptase polymerase chain reaction, SET-NUP214 = proto-oncogene -nucleoporin 214.

Keywords: acute leukemia, allogeneic hematopoietic stem cell transplantation, Measurable residual disease, overall survival, relapse, SET-NUP214 fusion gene

1. Introduction

The SET nuclear proto-oncogene (SET)-nucleoporin (NUP) 214 fusion gene is a marker of acute leukemia (AL), resulted from either cryptic t(9;9)(q34;q34) or del(9)(q34.11q34.13).[1–7] SET-NUP214 fusion gene was first detected in a patient with acute undifferentiated leukemia (AUL), and later detected in patients with acute myeloid leukemia (AML), T-cell acute lymphoblastic leukemia (T-ALL) and B-cell acute lymphoblastic leukemia (B-ALL).[2–7] The majority of patients carrying SET-NUP214 experience T-cell acute lymphoblastic leukemia (T-ALL). In
addition, previous studies supported a strong association between SET-NUP214 fusion gene and T-ALL. The detailed mechanism by which SET-NUP214 mediates leukemogenesis has not been fully elucidated to date. SET, also referred to as TATA box binding protein-associated factor 1, is a component of an inhibitor of histone acetyltransferase (INHAT), which participates in transcriptional activation. The NUP214 gene, also referred to as CAN, participates in development and possibly in leukemogenesis. SET-NUP214 rearrangement produces a fusion protein that inhibits the cell apoptosis caused by the cytotoxic T-cells.

Studies in the past have shown that genetic markers genetic markers are of great significance for the diagnosis and prognosis of malignant tumors.\cite{12,13} And measurable residual disease (MRD) is an important prognostic factor that can determine patients at a high risk for relapse, and interventions directed by MRD could decrease the incidence of relapse.\cite{14,15} The measurement of leukemia specific fusion transcript levels obtained via real-time quantitative polymerase chain reaction (RQ-PCR) could accurately and sensitively reflect MRD status. SET-NUP214, a rare fusion gene for AL, has the potential to be a good marker for assessing MRD status. Previous studies have also suggested that SETNUP214-positive AL patients are associated with a poor prognosis.\cite{3,10} However, the number of reported cases with SET-NUP214 fusion gene was very limited. There are no specific clinical studies to analyze the clinical significance of SET-NUP214 fusion gene for monitoring MRD status and predicting relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Whether the SET-NUP214 fusion gene could serve as a biomarker for MRD surveillance after transplantation needs to be further confirmed.

In this study, we investigated a consecutive cohort of SET-NUP214-positive (SET-NUP214+) AL patients who received allo-HSCT at our institute. Their SET-NUP214 gene was examined by RQ-PCR at specific time points after transplantation. The correlation between SET-NUP214 expression levels and other current MRD markers, including leukemia-associated immunophenotypes (LAIPs) and leukemia relapse, were analyzed. Our research aimed to observe the dynamic changes in SET-NUP214 expression before and after allo-HSCT and analyze whether SET-NUP214 is a suitable marker for evaluating MRD status after allo-HSCT.

2. Material and methods

2.1. Study patients and design

We retrospectively analyzed a total of 24 AL patients who were newly diagnosed with SET-NUP214 fusion gene at Peking University Institute of Hematology from March 2012 to April 2018 and had all received allo-HSCT. Patients were diagnosed using the current, widely used WHO criteria.\cite{16} Leukemia relapse was scored as BM, extramedullary, or both using previously described common morphological criteria.\cite{17} The study design adhered to the principles of the Helsinki Declaration and was approved by the Peking University Institute of Hematology. Nine patients who received HLA-matched sibling donor transplantation (MSDT) and 15 patients who received unmanipulated haploidentical HSCT (haplo-HSCT) were enrolled in this study. Patient characteristics are shown in Table 1.

| Table 1 |
| Patient characteristics. |
| Characteristics | Cases |
| --- | --- |
| Median age (range), years | 27.5 (13–58) |
| Sex, male (n, %) | 19 (79.2%) |
| Median SET-NUP 214 level, median (range) | 405.1% (14.6–1482.4%) |
| Disease status (n, %) |  |
| CR1 | 22 (91.6%) |
| CR2 | 1 (4.2%) |
| NR | 1 (4.2%) |
| FAB subtype (n, %) |  |
| T-ALL | 13 (54.2%) |
| B-ALL | 3 (12.5%) |
| AML | 6 (25%) |
| AUL | 2 (8.3%) |
| Transplant type (n, %) |  |
| Haploidentical | 15 (62.5%) |
| Sibling-identical | 9 (37.5%) |
| Leukemia relapse (n, %) | 5 (20.8%) |
| Death (n, %) | 6 (25%) |
| Die of relapse | 3 (12.5%) |
| Treatment-related death | 3 (12.5%) |

2.2. Transplant procedures

The enrolled patients in this study received myeloablative conditioning regimens, and unmanipulated haplo-HSCT and HLA-identical sibling donor transplantation were reported as previously described.\cite{18–20} The patients who had a HLA-mismatched donor were conditioned with cytosine arabinoside (Ara-C; 4g/m²/d), on days –10 and –9), busulfan (BU, 3.2mg/kg/d iv, on days –8 to –6), cyclophosphamide (CTX, 1.8g/m²/d, on days –5 and –4), 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Me-CCNU, 250mg/m², once on day -3) and rabbit antithymocyte globulin (ATG, Sang Stat, Lyon, France; 2.5 mg/kg/d). Patients with identical donors received a regimen described above except that MSDT patients received hydroxyurea (80 mg/kg total dose), a lower dose of Ara-C (2g/m²/d), and no ATG. All patients received a mixture of allografts including granulocyte colony-stimulating factor (G-CSF; 5 mg/kg/d for 5 days) primed peripheral blood (G-PB) and bone marrow (G-BM). Unmanipulated BM (harvested on day 4 after G-CSF) and PB stem cells (PBSCs, harvested on day 5 after G-CSF) were infused into the recipient on the day of collection. Prophylaxis against graft-vs-host disease (GVHD) included treatment with cyclosporine A and short-term methotrexate along with mycophenolate mofetil.

2.3. Donor lymphocyte infusion

Donor lymphocyte infusion (DLI) was performed as previously described.\cite{19–21} The indications for DLI included hematological leukemia relapse, receiving chemotherapy followed by DLI, or molecular test results that provided evidence of persistent leukemia or relapse in subjects GVHD, and graft failure. For relapse prophylaxis, only DLI was used.\cite{22}

2.4. Analysis of SET-NUP214 fusion gene

The SET-NUP214 fusion transcript was detected using TaqMan based RQ-PCR. RQ-PCR was performed using BM samples in all cases. The ABL1 was selected as the control gene to compensate
for variations in the quality and quantity of the RNA and cDNA. The transcript levels were calculated as the number of target transcript copies/the number of ABL1 copies and expressed as a percentage.

2.5. Study definitions

The primary study end point was the cumulative incidence of leukemia relapse (CIR). The secondary end points were the overall survival (OS). Relapse, OS and MRD were defined as previously described. Any measurable MRD level was considered positive. A positive result of multicolor flow cytometry (FCM) was defined as the presence of a LAIP phenotype in $>0.01\%$ of cells in 1 of the BM samples from the AML patients. The pre-transplant SET-NUP214 measurement was performed using BM samples within a month before transplant as a routine. The post-transplant scheduled time points were +1, +2, +3, +4.5, +6, +9, and +12 month post-HSCT and every 6 months thereafter. More frequent MRD monitoring was performed in some patients depending on their individual intention. The SET-NUP214 transcript level greater than 0 was defined as positive.

2.6. Statistical analyses

Statistical analyses were performed using SPSS 24.0 (Chicago, IL). The CIR and OS were analyzed using Kaplan-Meier survival curves. Differences in the CIR and OS between groups were compared using the log rank test. Receiver operating characteristic (ROC) analysis was performed using the SPSS 24.0 software. A two-sided $P$ value of .05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Our study enrolled 24 AL patients with positive SET-NUP214 (SET-NUP214+) at the newly diagnosed, including 19 males and 5 females, with a median age of 28 years (13–58 years). The 24 AL patients included 13 cases (54.2%) of T-ALL, 2 cases (8.3%) of AUL, 6 cases (25%) of AML and 3 cases (12.5%) of B-ALL. They received MSDT ($n=9$) or haplo-HSCT ($n=15$), respectively. All patients acquired stable neutrophil engraftment. The date of May 31, 2019 was defined as the end of the follow-up period. The median follow-up time was 501 days (56–2208 days). Of the enrolled patients, 6 (25%) patients died, including three (12.5%) patients died of leukemia relapse. A total of 5 (20.8%) patients experienced hematological relapse at a median of 225 days (56–1057 days) post-transplantation. The median SET-NUP214 expression level at diagnosis was 405.1% (14.6%–1482.4%), and the median SET-NUP214 expression level before transplantation was 0.007% (0–73.9%). The characteristics of the enrolled patients are summarized in Table 1.

3.2. SET-NUP214 fusion gene expression before transplantation

Among the 24 patients, 11 patients were SET-NUP214 negative (SET-NUP214-), while the other 13 patients had a SET-NUP214 median expression level of 2.7% (0.0054%–73.9%) before allo-HSCT. Eight of these 13 SET-NUP214+ patients pre-transplantation still had a SET-NUP214+ expression after transplantation, while only 4 of 11 SET-NUP214- patients pre-transplantation became SET-NUP214+ after transplantation. The Kaplan-Meier survival curves analysis showed that there was an upward trend, but there was no statistical difference, the SET-NUP214+ group had a 2-year CIR of 24.2±15.6% vs 16.1±10.4% in the SET-NUP214- group pre-transplantation ($P=0.808$, Fig. 1A). Furthermore, our results showed the 2 groups had no significant differences in 2-year OS (71.4±14.4% vs 79.5±13.1%, respectively, $P=.628$, Fig. 1B). We further analyzed data by using the receiver operating characteristic (ROC) curve and turned out that the area under the ROC curve (AUC) was 0.569, this result showed that pre-transplantation SET-NUP214 gene expression level could not effectively predict relapse post-transplantation (95% CI: 0.285–0.854; $P=.670$, Fig. 1C).

3.3. SET-NUP214 fusion gene expression after transplantation

A total of 12 (50.0%) patients experienced a positive SET-NUP214 gene expression at a median of 90 days (30–270 days) after transplantation. The median expression level of SET-NUP214 in the first positive sample post-transplantation was 0.0845% (0.0028%–7.5%). Five of the 12 patients suffered from leukemia relapse during our follow-up period. Notably, of the 5 relapsed patients, 3 had previous SET-NUP214+ expression.
results before leukemia relapse, 1 patient had a long interval between the last detection of SET-NUP214 and the time of relapse. Another patient had SET-NUP214+ and FCM+ in a long interval after relapse. Those of SET-NUP214+ post-transplantation had a higher 2-year CIR of 43.7 ± 18.8%, while none of patients relapsed in SET-NUP214- group after transplantation ($P$ = .009, Fig. 2A). There was no significant difference between these 2 groups of patients with regard to their 2-year OS (82.5 ± 11.3 vs 64.6 ± 17.5%, respectively, $P$ = .271, Fig. 2B).

To further analyzed the significance of SET-NUP214 for predicting relapse, ROC curve analysis was performed on the SET-NUP214 expression levels that was firstly detected after transplantation. The result turned out that the AUC was 0.916 (95% CI: 0.784–1.0; $P$ = .005; Fig. 2C). The optimal cut-off point to predict inevitable relapse is 0.02%. It meant that SET-NUP214 expression levels higher than 0.02% might indicate subsequent relapse post-transplantation. Indeed, among the 12 patients with SET-NUP214+ after transplantation, the SET-NUP214 expression level of the 5 relapsed patients were all higher than 0.02%, and only 4 of the 7 no-relapsed patients were higher than 0.02%.

3.4. SET-NUP214 expression and FCM results after transplantation

To further evaluate whether the SET-NUP214 fusion gene monitored by RQ-PCR could serve as a specific MRD monitoring indicator and is better than FCM, we compared the pre-transplant SET-NUP214 expression and leukemia-associated immunophenotype (LAIP) monitored by multiparameter flow cytometry (FCM), which is another reliable MRD monitoring indicator for AL patients. The MRD status of 12 patients with SET-NUP214 gene expression after transplantation is shown in Figure 3. As the result shows, only 2 of the 12 SET-NUP214+ patients after transplantation showed FCM positive during MRD monitoring. Four of five relapsed patients post-transplantation had SET-NUP214+ expression before relapse, while all the 5 relapsed patients were FCM- before relapse (Patient 1, 2, 3, 4, and 5 in Fig. 3). It seemed that the fusion gene is positive earlier than LAIP and could predict recurrence earlier.

3.5. Intervention and prognosis of relapsed patients after transplantation

We analyzed the efficacy of intervention treatment in 12 patients with MRD positive. When MRD is positive, patients were given timely intervention therapy of interferon and chemotherapy followed by DLI. Among those 5 relapsed patients, one was treated with interferon when MRD was positive, and chemotherapy followed by DLI were given to further prevent relapse, but the patient both finally relapsed and died. One patient who experienced relapse at 36 months after transplantation was treated with chemotherapy followed by DLI, achieving remission, but relapsed again and eventually died of relapse. Another patient relapsed early after transplantation and died on the 6 day after relapse. The other two patients were treated with chemotherapy followed by DLI, they finally achieved remission and the SET-NUP214 fusion gene was negative.

4. Discussion

SET-NUP214 is a rare leukemia fusion gene. Due to the limited number of SET-NUP214-positive AL patients, no report has focused on the predictive significance of SET-NUP214 expression (before and after transplantation) on leukemia relapse after transplantation. In our study, we accumulated 24 consecutive SET-NUP214-positive AL patient cases over 6 years, and they all received allo-HSCT at our institute. As far as we know, this was the largest allo-HSCT cohort of SET-NUP214-positive AL patients in a study concerning MRD status monitoring. We aimed to investigate whether the SET-NUP214 fusion gene is a suitable marker for MRD monitoring. Our study suggested that the SET-NUP214 gene had implications for predicting relapse in MRD monitoring after transplantation.

Previous studies have demonstrated that MRD monitored either by LAIPs or leukemia-specific fusion gene levels before transplantation was an independent risk factor for disease relapse.[23,24] Abdelali et al used LgH/TCR rearrangement by PCR which sensibility would be able to reach $10^{-4}$–$10^{-5}$, in their study to demonstrate that the prognosis between SET-NUP214-positive and SETNUP214-negative patients before transplantation was not statistically significant, but 3-year the event-free survival (EFS) were higher in the SET-NUP214-negative patients.[3] Similarly, our results showed that the SET-NUP214-positive patients pre-transplantation tended to have a higher CIR and shorter OS, although there were no statistical differences (16.1% vs 24.2% for 2-year CIR; 71.4% vs 79.5% for 2-year OS) (Fig. 1). Most studies suggest that pre-transplant MRD positive predicts a poor prognosis after transplantation.[14,15,26,27] However, previous and our researches showed
the survival of SET-NUP214-positive patients was similar to that of SET-NUP214-negative patients. The above results may have the following explanations.

First, this MRD indicator is very sensitive, the low level of SET-NUP214 fusion gene before transplantation may not predict a recurrence. It is possible that SET-NUP214 fusion gene of patients, especially those who have undergone allo-HSCT, could turn negative under the influence of autoimmune immunity. Thus, it may have no significant effect on prognosis. Second, allo-HSCT can overcome the adverse effects of MRD positive to some extent before transplantation for AL patients. Huang et al demonstrated that the 5-year OS of T-ALL patients with chemotherapy and allo-transplantation was 9% and 38%, respectively. Abdelali et al showed that the OS at 3 years of SET-NUP214-positive patients was not significant different from that of SET-NUP214-negative patients (73% vs 68%; \( P = .86 \)). Our study also showed that pre-transplant AL patients with SET-NUP214 gene positive and negative had a similar prognosis (Fig. 1) and the OS rate of SET-NUP214 positive patients was superior to the previously reported OS rate. Therefore, it indicated that the allogeneic transplantation system of our institute may improve the survival of SET-NUP214-positive AL patients to some extent, and it may also overcome the adverse effect of pre-transplant MRD positive on prognosis. Of course, the number of SET-NUP214-positive patients is limited, and the exact conclusion requires a large sample of cases to confirm.

The data in this study suggested that the SET-NUP214 fusion gene could be a specific and sensitive MRD biomarker. In our study, SET-NUP214-positive patients after transplantation have significantly higher CIR and lower OS than SET-NUP214-negative patients (Fig. 2). SET-NUP214 fusion gene was highly expressed at the initial diagnosis, then gradually changed to the negative or low-level expression before transplantation. It would be positive again before recurrence after transplantation. This dynamic change was basically consistent with clinical performance, tumor burden status and another MRD monitoring marker such as LAIP. Furthermore, our results showed SET-NUP214 expression became positive before relapse and prior to flow cytometry results, and the result indicated that molecular detection is more sensitive than FCM. Considering the dynamic change of SET-NUP214 gene expression and the tumor doubling time, monthly bone marrow monitoring was required at an early-stage after transplantation. Previous studies have shown that the overall long-term survival rate of ALL is 30% to 60%. The MRD monitoring markers are useful for early intervention for relapse to improve prognosis of patients. Yan et al showed in their study that MRD-positive AL patients were treated with chemotherapy followed by DLI, and the 3-year CIR, 3-year disease-free survival (DFS) and 3-year OS of these patients reached 26.4%, 51.2% and 60.5%, respectively. In our study, the 3-year OS of 12 patients who were treated with chemotherapy followed by DLI reached 64.6%. This result suggested that early intervention in SET-NUP214-positive AL patients after...
transplantation was effective and could further improve the overall outcome.

5. Conclusion
In conclusion, we have explored the reliability of the SET-NUP214 fusion gene as a sensitive and specific MRD indicator for the AL patients received allo-HSCT in our study. SET-NUP214 fusion gene is associated with poor prognosis and early relapse intervention based on SET-NUP214 expression might further improve the therapeutic effect. Of course, the number of patients with SET-NUP214 fusion gene AL in our study is limited. It still needs a continuous study of accumulating more samples to more clearly demonstrate the dynamic changes of SET-NUP214 expression before and after transplantation.

Author contributions
Conceptualization: Xiao-Su Zhao.
Data curation: Meng-Ge Gao.
Funding acquisition: Xiao-Su Zhao.
Methodology: Xiao-Su Zhao.
Project administration: Xiao-Su Zhao.
Resources: Xiao-Su Zhao.
Software: Meng-Ge Gao.
Supervision: Xiao-Jun Huang.
Writing – original draft: Meng-Ge Gao.

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