


CASE REPORT

Clinical implications of combination therapy with quizartinib and craniospinal irradiation for refractory acute myeloid leukemia positive for FMS-like tyrosine kinase 3-internal tandem duplication with central nervous system involvement

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Abstract

FMS-like tyrosine kinase 3-internal tandem duplication (*FLT3*-ITD) mutation-positive acute myeloid leukemia (AML) has a poor prognosis. We report the first case of successful bridge therapy of novel *FLT3* inhibitor, quizartinib, to umbilical cord blood stem cell transplantation for *FLT3*-ITD-positive AML-primary induction failure patients with central nervous system involvement.

KEYWORDS

acute myeloid leukemia, CNS involvement, *FLT3*, inhibitor, stem cell transplantation

1 | INTRODUCTION

Patients with acute myeloid leukemia (AML)-primary induction failure (PIF) require stem cell transplantation as a curative therapy.¹ On the contrary, quizartinib

and gilteritinib have been launched for the treatment of FMS-like tyrosine kinase 3-internal tandem duplication (*FLT3*-ITD) mutation-positive AML,² but there are no coherent reports in the literature on how to treat lesions or use these drugs in the presence of central nervous system

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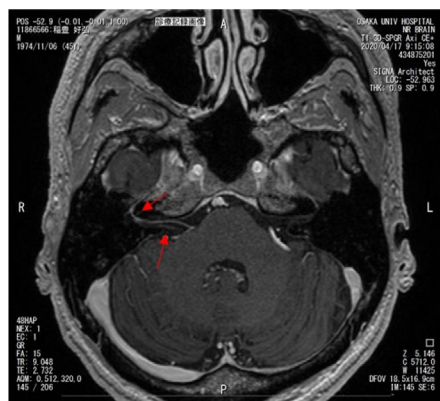
(CNS) involvement. We report a case of successful bridge therapy of quizartinib to umbilical cord blood stem cell transplantation (uCBT) for *FLT3-ITD*-positive AML-PIF patients with CNS involvement. A 40-year-old man presented to our hospital with fever. AML with PIF was diagnosed because it was refractory to induction therapy, and salvage chemotherapy was also ineffective. Because next-generation sequencing (NGS) mutational testing revealed *FLT3-ITD* positivity, oral quizartinib was initiated. Complete hematological remission (CR) was achieved 27 days after administering quizartinib. Intrathecal therapy and craniospinal irradiation were administered for CNS involvement. uCBT was successfully performed, and quizartinib maintenance therapy was administered. The quizartinib concentration was assessed during maintenance, and the concentration in plasma was considered optimal but unmeasurable in the spinal fluid. Hence, quizartinib was ineffective for CNS infiltration because of its penetration incapability across the brain–blood barrier. Therefore, quizartinib administration with craniospinal irradiation is considered a promising option for successful bridging to uCBT to cure AML-PIF patients with CNS infiltration.

2 | CASE REPORT

A 40-year-old man with fever presented to our hospital. Blood test results revealed leukocytosis and thrombocytopenia, and AML was diagnosed. A contrast-enhanced MRI of the head and the number of abnormal cells that led to the diagnosis of CNS involvement are shown in Figure 1.

Induction therapy comprising idarubicin and cytarabine was administered; however, the disease progressed quickly. Therefore, we diagnosed the patient as having AML with PIF (Figure 2). Simultaneously, facial nerve paralysis was observed. Neuropathy, craniospinal fluid (CSF) examination, and enhanced magnetic resonance imaging with gadolinium enhancement revealed central

nerve infiltration in AML cells. Combination therapy with mitoxantrone, etoposide, and cytarabine was initiated as re-remission induction therapy. The symptoms were slightly alleviated by the combined use of intrathecal methotrexate (MTX) and cytarabine. Although several intrathecal chemotherapies were administered, residual tumor cells remained in the CSF. Therefore, we conducted craniospinal irradiation (CSI) (14.4-Gy and 9-Gy boosts to the whole brain) for disease control of CNS involvement, which was successful. In contrast, NGS mutational testing revealed *FLT3-ITD* and nucleophosmin (*NPM1*) positivity; thus, we initiated oral administration of quizartinib together with CSI. The initial dose was 26.5 mg, which was later increased to 53 mg after confirming that the side effects were tolerable. CR was achieved 27 days after administering quizartinib. Although QTc elongation was observed as an adverse effect of quizartinib, it was acceptable to continue quizartinib. uCBT has been successfully performed in patients with CR under disease control. The patient was administered a myeloablative conditioning regimen comprising cytarabine (4 g/m²), fludarabine (150 mg/m²), busulfan (12.8 mg/kg), and total-body irradiation 4 Gy. The graft-vs.-host disease prophylaxis included tacrolimus and short-term MTX. Stomatitis (Grade III) was observed; however, it improved with blood cell recovery. Neutrophil engraftment was achieved on Day 21. Complete donor chimerism was achieved on Day 27 of remission. On Day 56, quizartinib (17.7 mg) was resumed, and CR was maintained for 1 year. In the steady state of quizartinib administration, the serum trough level was 163.3 ng/ml and the CSF trough level was below the detection limit of 10 ng/ml. At the time of quizartinib administration, *NPM1* gene mutation, a surrogate marker, was measured using polymerase chain reaction (PCR). Although *NPM1* in bone marrow was 2357.43 (*NPM1* mut/*ABL*, %) at the time of PIF, it was below detection sensitivity after uCBT. These results suggested that molecular genetic remission was achieved.



【Spinal tap test】

Abnormal cells	6 / μ L
Lymphocyte	1 / μ L
Monocyte	5 / μ L
Protein	41 mg/dL

【Cytologic analysis】

Class V
Atypical cells with prominent lobes

FIGURE 1 CNS involvement.

Contrast-enhanced MRI of the head showed contrast effects in the bilateral facial nerves (red arrows) and an increase in the number of abnormal cells, which led to the diagnosis of CNS involvement

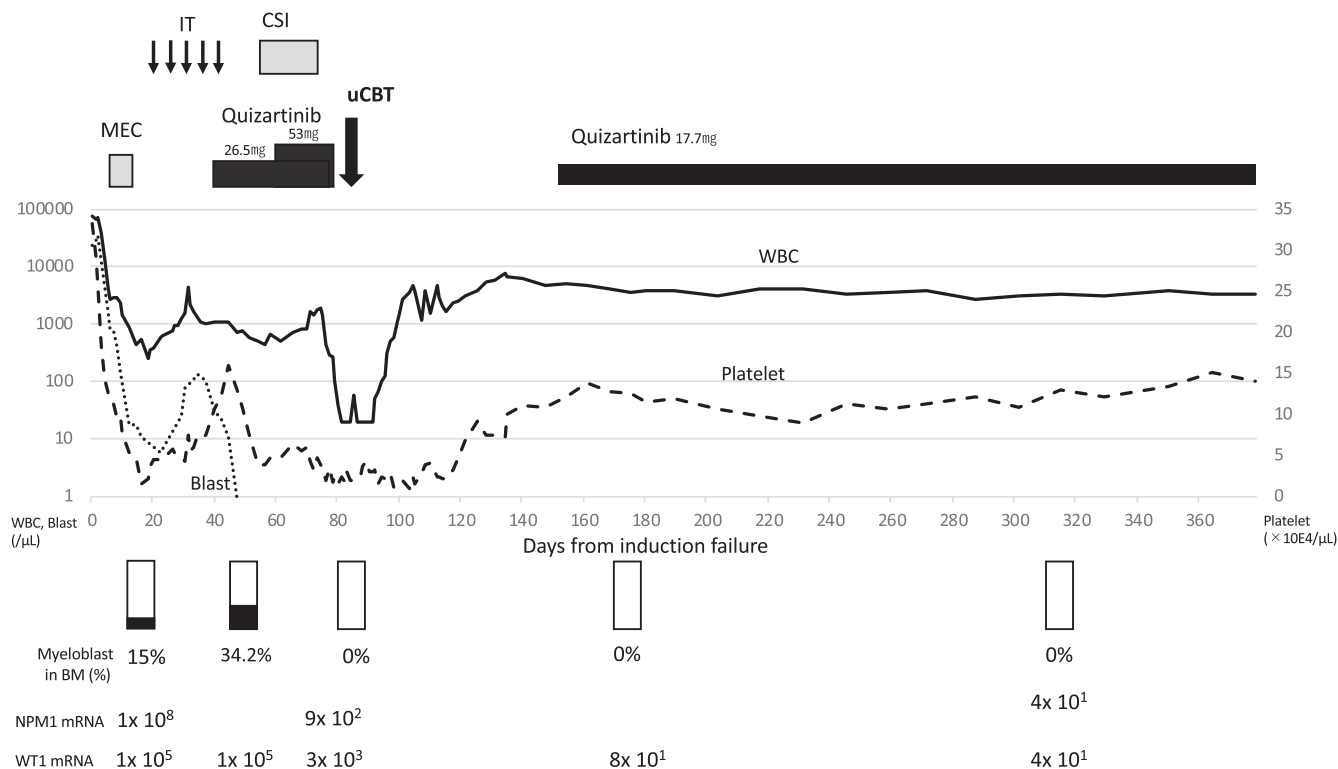


FIGURE 2 Clinical course. After the patient was diagnosed with PIF, salvage chemotherapy comprising MEC was administered; however, the disease progressed. The FLT3 inhibitor quizartinib was administered during the pretransplant period. Simultaneously, CSI was started. The patient successfully achieved molecular remission after uCBT. BM, bone marrow; CNS, central nervous system; CSI, craniospinal irradiation; IT, intrathecal methotrexate [MTX], cytarabine [Ara-C]; MEC, mitoxantrone, etoposide, Ara-C; PIF, primary induction failure; qPCR, quantitative polymerase chain reaction; uCBT, unrelated umbilical cord blood transplantation

2.1 | Measurement of quizartinib concentration

Quizartinib concentrations in the serum and spinal fluid were measured using liquid chromatography-tandem mass spectrometry (MS) (LCMS-8040, Shimadzu). MS/MS analysis was performed using an electron spray ionization source in the positive mode. Detection was performed by monitoring the ion transition of gilteritinib from m/z 561.2 to 421.0. A calibration curve was constructed using the external calibration curve method. The calibrator levels were 10, 30, 100, 300, 1000, and 3000 ng/ml.

2.2 | Genome profiling assay

We performed a comprehensive genome profiling assay for patients with relapsed and refractory and newly diagnosed unfit AML using the Foundation One Heme panel, as a part of Hematologic Malignancies (HM)-SCREEN-Japan 01 (UMIN000035233), a multicenter study.

3 | DISCUSSION

FLT3 is a type 3 receptor tyrosine kinase similar to KIT, FMS, and platelet-derived growth factor receptors.³ The FLT3 mutation is one of the typical genetic abnormalities observed in approximately 20%–30% of AML cases.⁴ In particular, internal tandem duplication (ITD) mutations are poor prognostic factors. However, not only ITD mutations but also tyrosine kinase domain (TKD) mutations are reported to constitutively activate the downstream RAS, PI3K, and STAT5 pathways and contribute to the promotion of leukemia growth.^{5,6} Recently, two FLT3 inhibitors, gilteritinib and quizartinib, have become clinically available in Japan. Therefore, the treatment strategy for FLT3 mutation-positive AML has changed significantly. Gilteritinib is a type 1 inhibitor of ITD and TKD mutations.⁷ Although quizartinib is a type 2 inhibitor effective against ITD mutations but not TKD mutations, there have been less reports of severe adverse effects (myelosuppression and QT elongation) following quizartinib administration.⁸ It is crucial to select a drug considering its characteristics and the profile of side effects. In this case, we had confirmed that

the patient did not have a TKD mutation. Allogeneic transplantation was performed as soon as possible after disease control with FLT3 inhibitors, and quizartinib was selected to induce an early response. In addition, quizartinib is highly selective, and we believed that the advantage of avoiding complications such as adverse reactions to off-targets might be an important issue in pretransplant patients.

QUANTUM-R, a randomized, double-blind, phase III trial of quizartinib, demonstrated the effectiveness of quizartinib over conventional chemotherapy in FLT3-ITD-positive AML patients.^{9,10} Moreover, many cases underwent hematopoietic cell transplantation in the quizartinib group compared to those in the chemotherapy group in a sub-analysis.¹¹

The optimal dose was not determined after transplantation because CYP3A4 inhibitors such as calcineurin inhibitors and triazole antifungal agents were frequently used in combination with the post-transplantation phase.¹² In this case, we administered quizartinib at 17.7 mg daily, which was one-third of the standard dose (53.3 mg qd [once daily]) in combination with fluconazole and tacrolimus. A phase I study reported that 60 mg of quizartinib hydrochloride was the limiting dose in post-transplant maintenance therapy.¹³ Moreover, Usuki et al. reported regarding a phase I Japanese subset in which the serum trough level of quizartinib was 40.9 ng/ml at 20 mg qd, 37.2 ng/ml at 30 mg qd, and 137 ng/ml at 60 mg qd.¹⁴ In this case, the administration of 17.7 mg qd quizartinib (quizartinib hydrochloride 20 mg) could be continued without adverse events such as QT prolongation and cytopenia while achieving optimal quizartinib concentrations in the serum.

Clinical trials on quizartinib have excluded cases with CNS infiltration, and there are no data on the transfer of quizartinib to the CNS.^{11,13,15,16} In this study, we measured quizartinib concentrations in the serum and spinal fluid and found that the concentration in the peripheral blood was sufficient. However, the concentration in the spinal fluid was undetectable. It is challenging to control CNS lesions with quizartinib alone when CNS involvement is present, as in this case. We considered it essential to control the disease by whole-brain and whole-spinal cord irradiation before transplantation. In contrast, it has been confirmed that venetoclax can be transferred to the CSF in a small number of cases and may be a treatment option for AML with CNS involvement in the future.¹⁷ At present, it has not been investigated whether FLT3 inhibitors migrate to the central nervous system. Only a recent case report has shown that gilteritinib is effective in treating patients with CNS involvement.¹⁸ In the future, it will be important to find out which FLT3 inhibitors can be

expected to be transferred to the CNS, and if they are not expected to be transferred to the CNS, it will be important to select them appropriately, such as in combination with radiation therapy or chemotherapy. FLT3-ITD-positive AML has a high risk of relapse, and an accurate evaluation of minimal residual disease (MRD) after transplantation helps predict recurrence.^{19,20} MRD detection by standard quantitative PCR for FLT3-ITD mutation-positive AML is challenging because of PCR bias; therefore, novel MRD detection methods using NGS have been attempted. In this case, *NPM1* positivity was confirmed by the NGS comprehensive searching project, HM-SCREEN 01 Japan Study,²¹ when induction failure was diagnosed in the patient. Therefore, *NPM1* and Wilms tumor gene-1 (*WT1*) were considered candidates for MRD monitoring of the disease. The *NPM1* gene expression gradually decreased after administering quizartinib and was undetectable 6 months after transplantation. However, among the *NPM1* mutation-positive cases below the *NPM1*-MRD threshold, recurrent cases with FLT3-ITD positivity but *NPM1* negativity have been reported. Conversely, the *WT1* level is known to be a marker of non-specific leukemia disease activity and may help predict disease burden or relapse. In this case, we must pay attention to the discrepancy between *NPM1*-MRD and *WT1* mRNA. Moreover, FLT3 mutations such as F691L and D835V/Y sometimes emerged through the treatment. In such cases, quizartinib may not be effective. We could not measure additional mutations because quizartinib responded rapidly and remained effective during post-transplant maintenance therapy in this case. If the disease recurs or flares up during the disease, additional mutations should be considered, not only *NPM1* and *WT1* measurement.

4 | CONCLUSION

We report the first case in which quizartinib was significantly effective against AML with PIF, and CSI was simultaneously performed for CNS infiltration to avoid high-dose chemotherapy, which causes severe cytopenia. Quizartinib administration prior to stem cell transplantation is a promising bridging strategy; however, if the leukemic cells have infiltrated the central nervous system, appropriate combination therapy such as chemotherapy and radiation therapy should be considered, taking into account the spinal fluid transferability of FLT3 inhibitors.

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CONFLICTS OF INTERESTS

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

MS served as a major contributor in writing the manuscript. KF and TU analyzed and interpreted the patient data regarding hematological disease. YA and SN evaluated the concentration of drugs. YM provided the NGS sequence data. Others read and critically improved and approved the final manuscript.

ETHICAL APPROVAL

This observational study was approved by the institutional review board at the Osaka University Hospital (#13167, 16265) and conducted in accordance with the Declaration of Helsinki.

CONSENT

Written informed consent was obtained from the patient before specimen collection.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not openly available due to their containing information that could compromise the privacy of the research participants. The data are available from the corresponding author upon reasonable request.

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