Gilteritinib monotherapy as a transplant bridging option for high risk FLT3-mutated AML with t(6;9)(p23;q34.1);DEK-NUP214 in morphological but not cytogenetic or molecular remission following standard induction chemotherapy

James W Day\textsuperscript{a,b,*}, Thomas A Fox\textsuperscript{a,b}, Rajeev Gupta\textsuperscript{a}, Asim Khwaja\textsuperscript{a}, Andrew J Wilson\textsuperscript{a}, Panagiotis D Kottaridis\textsuperscript{a}

\textsuperscript{a} Department of Hematology, University College London Hospitals NHS Foundation Trust, London, United Kingdom
\textsuperscript{b} UCL Institute of Immunity and Transplantation, UCL, London, United Kingdom

\textbf{A B S T R A C T}

We report a case of FLT3-mutated AML with t(6;9) in which induction chemotherapy with DA and midostaurin failed to achieve complete cytogenetic or molecular remission. Due to the COVID-19 pandemic and co-existing cellulitis, monotherapy with the selective FLT3-inhibitor gilteritinib was used as an alternative consolidation treatment option rather than further intensive chemotherapy. Gilteritinib was able to achieve complete molecular and cytogenetic remission despite the additional cytogenetic abnormality. This case provides supporting evidence for the use of single agent gilteritinib in high-risk primary refractory FLT3-mutated AML with t(6;9) prior to transplantation.

\section{Introduction}

In acute myeloid leukemia (AML), the presence of internal tandem duplications (ITD) in the juxta-membrane region of the \textit{fms} related receptor tyrosine kinase 3 (FLT3) gene is a poor prognostic marker at diagnosis \cite{1} and in refractory or relapsed cases \cite{2,3}. The oral FLT3 tyrosine kinase inhibitors (TKI) midostaurin and gilteritinib are licensed for use in the upfront and relapsed/refractory setting respectively in FLT3-mutated AML. A number of cytogenetic abnormalities are also linked to poor prognosis in AML, including the t(6;9)(p23;q34.1) translocation, which occurs in 1–2\% of all AML cases and is frequently found with a FLT3-ITD mutation. This recurring aberration results in the formation of the chimeric fusion gene DEK-NUP214, which alters nuclear transport and results in increased myeloid protein synthesis \cite{4}; it is associated with resistance to intensive chemotherapy and a higher risk of relapse, independent of the FLT3-ITD mutation \cite{5}. Allogeneic hematopoietic stem cell transplantation (alloHCT) in first complete remission (CR) substantially improves otherwise dismal outcomes \cite{6}.

In AML, the addition of a FLT3 inhibitor to induction chemotherapy has become the standard of care when a FLT3 mutation is detected at diagnosis. We describe a patient with AML with t(6;9) and a FLT3-ITD, treated at University College Hospital, London (UCLH) between January and May 2020, with persistent disease following induction chemotherapy plus midostaurin. Gilteritinib monotherapy was used as second line treatment, instead of salvage chemotherapy, in order to minimize the duration of aplasia as the patient had severe cellulitis as well as to reduce risk from the ongoing COVID-19 pandemic.

\section{Case report}

A previously fit and well 40 year old female presented to her local hospital with severe peri-orbital cellulitis, anemia and thrombocytopenia (Hemoglobin 65 g/L, platelet count 41 × 10\(^9\)/L). The total white cell count was 13.75 × 10\(^9\)/L, with a neutrophil count of 8.8 × 10\(^9\)/L and blasts of 2.75 × 10\(^9\)/L. Bone marrow biopsy demonstrated 60\% myeloid blasts. T(6;9)(p23;q34.1) was detected in all metaphases by G-banding; fluorescent in-situ hybridization (FISH) for the DEK-NUP214 fusion gene was positive in 92\% of cells, suggesting that the AML blast population may have arisen from an antecedent DEK-NUP214 positive clone in the context of a previously undiagnosed MDS/MPN syndrome. A FLT3-ITD of 93 nucleotide length was detected with a variant allele frequency (VAF) in the peripheral blood of 38\% - as only 20\% of the WBC were blasts, this was consistent with the presence of FLT3-ITD in the non-blast population.
The patient was transferred to UCLH where induction chemotherapy with daunorubicin 60 mg/m² and cytarabine 100 mg/m² bd in the 3 + 10 regimen was started. Midostaurin, 50 mg twice daily was commenced 24 h after the last dose of chemotherapy and continued for 14 days as standard. On day 25 post-induction chemotherapy, there was neutrophil and platelet recovery and bone marrow examination showed morphological and flow cytometric complete remission (CR). However, FISH was positive for DEK-NUP214 in 32% of cells and quantitative polymerase chain reaction (qPCR) showed only a 1-log reduction in DEK-NUP214 transcripts compared to the diagnostic sample. The FLT3-ITD was still detectable with a VAF of 14%. These findings indicated that, despite the morphological CR and recovery of neutrophils and platelets, the induction regimen had failed to eliminate the pre-leukemic clone which remained positive for both the cytogenetic and FLT3 lesions, despite treatment including midostaurin.

Because of ongoing extensive cellulitis requiring surgery and the risks of delivering further intensive chemotherapy at the height of the COVID-19 pandemic, consolidation therapy with the potent, selective FLT3 inhibitor, gilteritinib was started. The patient remained well during treatment, was blood product transfusion-independent and did not require hospital admission. After eight weeks of treatment with gilteritinib, repeat bone marrow examination demonstrated morphological, cytogenetic and molecular complete remission. The patient continued on single-agent gilteritinib and subsequently underwent an HLA matched unrelated hematopoietic stem cell transplantation (alloHSCT). The patient remains well in complete remission 16 months post-transplant.

3. Discussion

This case shows that gilteritinib monotherapy can be used to achieve complete molecular and cytogenetic remission in t(6;9) DEK-NUP214 AML with a FLT3 mutation. This therapy was delivered in an outpatient setting, demonstrated good tolerability and significantly less toxicity than the current standard of care for consolidation high-dose chemotherapy regimens. A previously reported case in the literature demonstrated that a different FLT3 inhibitor, sorafenib, in combination with a hypomethylating agent, azacitidine, was able to induce remission in a patient with chemotherapy-refractory t(6;9) and FLT3 positive AML [7]. Other TKIs have been used in the relapsed setting with mixed results. In a large cohort study of adult patients with AML with t(6;9), seven patients who had relapsed either post alloHSCT or post-chemotherapy were treated with some form of TKI, either in isolation or in combination with chemotherapy. This failed to achieve a response in the majority of patients; however one patient treated with gilteritinib monotherapy did achieve a second complete remission [6].

An interesting feature of this case is that induction therapy markedly reduced the blast population, consistent with a morphological CR, but there was a high level of persistence of DEK-NUP214 by FISH and qPCR analyses and the FLT3-ITD was detectable at a level consistent with heterozygous expression in all remaining malignant cells. Although the acquisition of a FLT3 mutation is often considered to be a late event in AML pathogenesis, the achievement of complete FISH and molecular remission for DEK-NUP214 using gilteritinib monotherapy suggests that in this case, the FLT3-ITD was important in maintaining a pre-AML disease state, consistent with the FLT3 mutation being an early event.

Allogeneic HSCT has been shown to be crucial for achieving cure in DEK-NUP214 AML - the achievement of measurable residual disease negativity prior to HSCT markedly improves outcomes due to reduced post-transplant relapse rates [8]. This case shows that gilteritinib monotherapy can be used to achieve molecular remission in cytogenetic and molecular disease persistence with DEK-NUP214 and FLT3-ITD, without bone marrow suppression, making it a potentially useful option in patients with concomitant infection and those at risk from the Covid-19 pandemic.

Declaration of Competing Interest

None of the authors had relevant conflicts of interest to declare.

Acknowledgements

All authors had input on the writing of the paper and approved the final version of the manuscript prior to submission. P.D.K, A.W., R.G and A.K were in charge of the clinical care of the patient and were responsible for the treatment decisions.

References

[1] P.D. Kottaridis, R.E. Gale, M.E. Frew, et al., The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy; analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials, Blood 98 (6) (2001) 1752–1759. Sep 15.
[2] H. Kiyoi, T. Naoe, Y. Nakano, et al., Prognostic implication of FLT3 and N-RAS gene mutations in acute myeloid leukemia, Blood 93 (9) (1999) 3074–3080. May 1.
[3] P. Chevallier, M. Labopin, P. Turlure, et al., A new leukemia prognostic scoring system for refractory/relapsed adult acute myelogeneous leukaemia patients: a GOELAMS study, Leukemia 25 (6) (2011) 939–944. Jun.
[4] M. Ageberg, K. Drott, T. Ölofsson, et al., Identification of a novel and myeloid specific role of the leukemia-associated fusion protein DEK-NUP214 leading to increased protein synthesis, Genes Chromosom. Cancer 47 (4) (2008) 276–287. Apr.
[5] K. Tarlock, T.A. Alonso, P.P. Moraleta, et al., Acute myeloid leukaemia (AML) with t (6;9)(p23;q34) is associated with poor outcome in childhood AML regardless of FLT3-ITD status: a report from the children’s oncology group, Br. J. Haematol 166 (2) (2014) 254–259. Jul.
[6] S. Kayer, R.K. Hils, M.R. Lukin, et al., Allogeneic hematopoietic cell transplantation improves outcome of adults with t(6;9) acute myeloid leukaemia: results from an international collaborative study, Haematologica 105 (1) (2020) 161–169. Jan.
[7] Y. Song, D. Bixby, D. Roulston, et al., The challenge of t (6;9) and FLT3-positive acute myelogenous leukemia in a young adult, J. Leuk. (Los Angel) (2014) 2.
[8] M. Díaz-Beyá, M. Labopin, J. Maertens, et al., Allogeneic stem cell transplantation in AML with t(6;9)(p23;q34);DEK-NUP214 shows a favourable outcome when performed in first complete remission, Br. J. Haematol 189 (5) (2020) 920–925. Jun.