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Clonal evolution of AML on novel *FMS*-like tyrosine kinase-3 (*FLT3*) inhibitor therapy with evolving actionable targets

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ABSTRACT

For acute myeloid leukemia (AML), identification of activating mutations in the *FMS*-like tyrosine kinase-3 (*FLT3*) has led to the development of several *FLT3*-inhibitors. Here we present clinical and next generation sequencing data at the time of progression of a patient on a novel *FLT3*-inhibitor clinical trial (ASP2215) to show that employing therapeutic interventions with these novel targeted therapies can lead to consequences secondary to selective pressure and clonal evolution of cancer. We describe novel findings alongside data on treatment directed towards actionable aberrations acquired during the process. (Clinical Trial: NCT02014558; registered at: ⟨https://clinicaltrials.gov/ct2/show/NCT02014558⟩)

1. Introduction

The development of kinase inhibitors for the treatment of leukemia has revolutionized the care of these patients. Since the introduction of imatinib for the treatment of chronic myeloid leukemia, multiple other tyrosine kinase inhibitors (TKIs) have become available [1]. Additionally, for acute myeloid leukemia (AML), identification of activating mutations in the *FMS*-like tyrosine kinase-3 (*FLT3*) has led to the development of several *FLT3*-inhibitors [2–5]. The article herein reports a unique case of AML that underwent clonal evolution while on a novel *FLT3*-inhibitor clinical trial. Here we show that employing therapeutic interventions with these novel targeted therapies can lead to consequences secondary to selective pressure and clonal evolution of cancer. Personalizing therapy in realtime based on changing targets presents both as challenge and an opportunity. Our work herein presents clinical and next generation sequencing data at the time of progression to illustrate these important concepts stemming from Darwinian evolution [6]. We describe novel findings alongside data on treatment directed towards actionable aberrations acquired during the process.

2. Clinical course and management

Our work focuses on a 23-year-old male who presented with 3 months history of fatigue and easy bruising along with a 2 day history of fever and chest pain. Initial bloodwork revealed a white blood count of 22.0×10^9/L with 51% circulating blasts, hemoglobin 7.6 g/dL, and a platelet count of 43×10^9/L. A bone marrow biopsy confirmed a diagnosis of AML. Initial cytogenetic studies identified trisomy 8 in all the twenty metaphases examined. Mutational analysis revealed an internal tandem duplication of the *FLT3* gene (*FLT3-ITD*).

He received standard induction chemotherapy (7+3) with cytarabine (ARA-C; 100 mg/m^2 for 7 days) and daunorubicin (DNM; 60 mg/m^2 for 3 days). His induction chemotherapy was complicated by severe palatine and uvular necrosis of indeterminate etiology (possible mucormycosis), necessitating aggressive surgical debridement.

Bone marrow biopsy at day 28 demonstrated persistent disease with 10% bone marrow blasts (Fig. 1). Due to his complicated clinical course and the presence of a *FLT3-ITD*, salvage therapy with 5-azacitidine (5-AZA) and sorafenib (SFN) was instituted.

With the sorafenib and 5-azacitidine, he achieved morphological remission (< 5% blasts). His older brother was found to be a 10/10 HLA match. Subsequently, he underwent a reduced intensity conditioning matched-related donor stem cell transplant (MRD-HCT) with fludarabine and busulfan (FluBu) conditioning chemotherapy.

The patient unfortunately had relapse of his leukemia on day +67 after his allo-HCT (Fig. 1). Sorafenib was briefly reinitiated and then he enrolled in a novel *FLT3*-inhibitor (ASP2215) clinical trial (NCT02014558) [7]. To potentiate the graft-versus-leukemia (GVL) effect, he received a cryopreserved donor lymphocyte infusion (DLI) during cycle 4 of ASP2215.

Routine surveillance bone marrow biopsy during the fifth cycle (28 day cycle) of ASP2215 therapy demonstrated 5% bone marrow

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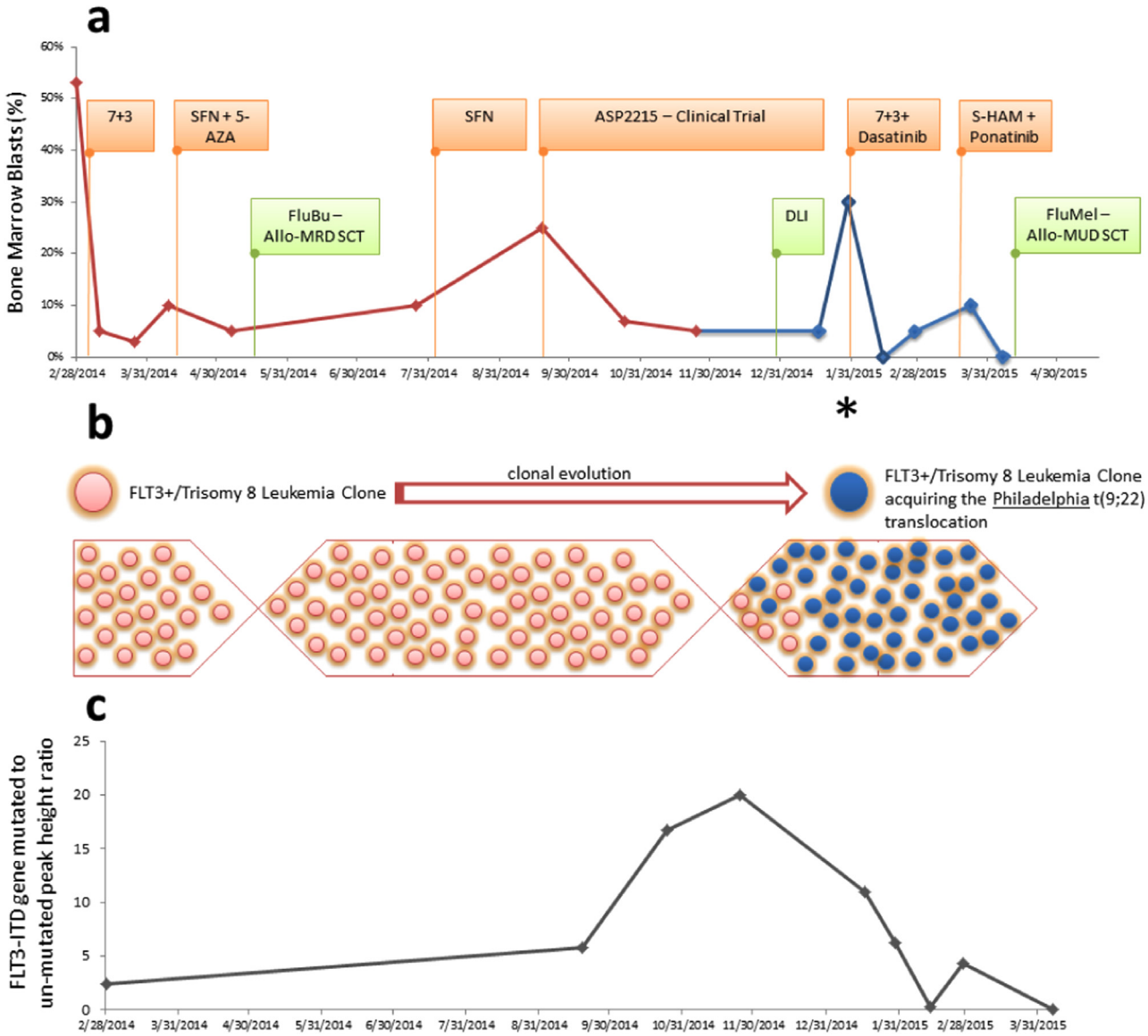

Fig. 1. Clinical course and various treatments received for our patient with FLT3+/trisomy 8 acute myeloid leukemia (AML). (a) The bone marrow blasts (%) are shown at different time points alongside the treatments received. (b) Schematic representation of selection pressure leading to development of a new clone of *FLT3*+/Trisomy 8 leukemia with the Philadelphia t(9;22) translocation. (c) The *FLT3-ITD* gene mutated to un-mutated peak height ratio is shown at different time points. Abbreviations: 7+3 - Induction chemotherapy with an anthracycline and cytarabine (see text for details/doses); SFN – Sorafenib; AZA – 5-Azacitadine; ASP2215 – Novel FLT3 inhibitor (NCT02014558); FluBu – Conditioning chemotherapy with fludarabine and busulfan; FluMel – Conditioning chemotherapy with Fludarabine and melphalan; MRD-SCT – Matched related stem cell transplant; MUD – SCT – Matched unrelated stem cell transplant; S-HAM – sequential high dose Ara-C chemotherapy with mitoxantrone.

blasts. Cytogenetic studies showed that of the 20 metaphases analyzed all had trisomy 8. However, initially 5 out of 20 and then later 20 out of 20 of these metaphases had also acquired the Philadelphia t(9;22) chromosomal translocation. His bone marrow aspirate/biopsy was also analyzed through a commercial next generation sequencing (NGS) assay (FoundationONE Heme) with results shown in Table 1. Salvage chemotherapy (7+3) was instituted with cytarabine (ARA-C; 100 mg/m^2 for 7 days) and Idarubicin (IDA; 12 mg/m^2 for 3 days) with the addition of dasatinib 100 mg per oral (PO) daily given the emergence of the *BCR-ABL1* clone (the new t(9;22) clone with p210 protein transcript).

He developed pneumonitis, pericarditis and rapid relapse following reinduction chemotherapy which prompted treatment with sequential-high dose cytarabine (ARA-C 3000 mg/m^2 days 1, 2, 8 and 9) and mitoxantrone (10 mg/m^2 days 3, 4, 10 and 11) [S-HAM] salvage chemotherapy to achieve aplasia prior to a second allogeneic transplant. Given that the patient's clone had both the *FLT3* and the *BCR-ABL1* aberrations ponatinib was added since it is a TKI with dual *FLT3* and *BCR-ABL1* inhibitory activity (Table 1). This was given at the standard dose of 45 mg PO daily for a week prior to chemotherapy and at a reduced dose of 15 mg daily during cytotoxic chemotherapy.

Subsequent bone marrow biopsy prior to the second transplant did not show any morphological or molecular evidence of leukemia. Patient, therefore, underwent conditioning chemotherapy with fludarabine and melphalan (FluMel) prior to a matched unrelated donor allogeneic transplant (MUD-SCT) (Fig. 1). This was complicated by pancreatitis requiring total parenteral nutrition and supportive care for several weeks. Following this, patient now has been transitioned to an outpatient setting with excellent signs of engraftment and is transfusion independent. Day 30, day 60 and now the 6 month chimerism studies show 100% donor and 0%