Somatic Sequencing Identifies Trametinib-Responsive Myelodysplastic Syndrome and Finds Acquired Clonal Hematopoiesis of Indeterminate Potential

INTRODUCTION

The MAPK pathway is constitutively activated in patients with low-grade myelodysplastic syndrome (MDS) and those with acute myeloid leukemia (AML).\(^1\)\(^2\) MEK is a unique protein in the MAPK pathway that serves as a convergence point for multiple upstream signal transduction pathways but is responsible only for the phosphorylation of ERK.\(^1\) Trametinib, an MEK inhibitor, has demonstrated clinical activity in metastatic melanoma.\(^4\) As a result of the clinical activity of trametinib and frequency of MAPK alterations in MDS/AML, trametinib therapy is being explored. A study of patients with myeloid malignancy compared the response rate of trametinib among patients with RAS wild-type (n = 30) and RAS-mutated MDS or AML (n = 50). Although the overall survival (OS) rate was similar between the cohorts, the overall response rate (ORR) was higher among cohorts with RAS mutation. Five patients with RAS-mutated MDS or AML achieved a complete response (CR) or CR with incomplete platelet recovery compared with no patients with RAS wild-type MDS or AML.\(^5\)

Herein, we describe a patient with relapsed MDS after undergoing allogeneic stem-cell transplant (allo-SCT) who had next-generation sequencing (NGS) identifying MAP2K2 P298L, for which the patient received trametinib plus decitabine and achieved a durable CR. The MAP2K2 P298L mutation has been identified previously in a patient with lung cancer, but the functional significance at the protein level has not yet been elucidated.\(^6\)

CASE REPORT

The patient is a 52-year-old Asian woman with a 12-year history of JAK2-negative essential thrombocythemia (ET) treated with anagrelide (10 years) and hydroxyurea (2 years). Twelve years after ET diagnosis, a bone marrow biopsy (BMBx) was repeated secondary to worsening anemia, thrombocytopenia, and constitutional symptoms. BMBx specimen morphology revealed increased trilineage dysplasia, 4% myeloblasts, and focal fibrosis consistent MDS/myeloproliferative neoplasm overlap syndrome. Cytogenetics were complex [45, XX, del(1)(q12), add(4)(q25), der(6)t(1;6)(q21;p23), -7, add(12)(p13), del(20)(q11.2)[cp16]/45, idem, -del(1)(q12), +der(1)add(1)(p36.1)del(1)(q12)]\(^4\). The patient received five cycles of azacitidine, and stable disease was achieved. She then proceeded with a matched related-donor allo-SCT from an older relative (> 60 years). Examination of a BMBx specimen 3 months after allo-SCT was consistent with a CR with 100% donor myeloid chimerism.

Six months after allo-SCT, examination of tissue from a repeated BMBx confirmed recurrent MDS/myeloproliferative neoplasm with complex cytogenetics [45, XX, der(1)add(1)(p36.1) del(1)(q12), add(4)(q25), der(6)t(1;6)(q21; p23), -7, add(12)(p13), del(20)(q11.2)[cp5]/46, XX[15]] and partial loss of chimerism on the myeloid cells (58%). Approximately 7.8 months after allo-SCT, a peripheral blood (PB) sample was submitted for NGS analysis by Genoptix NexCourse Complete (Carlsbad, CA). The NGS results (Data Supplement), returned 8.5 months after the allo-SCT, reported several pathogenic...
mutations, notably *RUNX1 S141* (mutation allele frequency [MAF], 12%), *ZMYM3 G49Wfs*13 (MAF, 27%), *CALR K368Rfs*51 (MAF, 39%), and *MAP2K2 P298L* (MAF, 30%). Owing to the *MAP2K2* mutation and lack of standard treatment options, the Moffitt Clinical Genomics Action Committee recommended trametinib at 8.7 months after allo-SCT. A BMBx specimen obtained 9.2 months after allo-SCT was significant for complete loss of chimerism on the myeloid cells (0%). In addition, the patient developed progressive cytopenias requiring transfusions. At 9.8 months after allo-SCT, the tacrolimus dose was tapered and she was prescribed decitabine 20 mg/m² intravenously on days 1 through 5 of a 28-day cycle; oral trametinib 2 mg daily was added 1 month later after resolution of typhlitis.

Two months after the initiation of combination therapy, a rash and severe oral and vaginal mucositis developed; trametinib and decitabine were temporarily held. A skin biopsy specimen was positive for graft-versus-host disease (GVHD) and the patient’s condition was treated with a steroid taper and immunosuppressive medications. After a 1-month treatment interruption, the mucositis resolved and treatment resumed with decitabine 20 mg/m² intravenously on days 1 through 5 of a 28-day cycle and trametinib 2 mg daily for 21 days of a 28-day cycle. Eight months into combination treatment, a 3-month interruption of decitabine occurred because of typhlitis, fungal pneumonia, neutropenic fever. At 10 months, a 1-month interruption of trametinib was initiated for grade 2 transaminitis. After resolution, treatment with decitabine 20 mg/m² intravenously on days 1 through 5 of a 28-day cycle and trametinib 0.5 mg daily for 7 days of a 14-day cycle continued without additional issues. Specimens obtained from repeated BMBx at 4, 9, and 14 months after starting combination therapy showed absence of overt dysplasia, normal cytogenetics, 100% donor-derived chimerism, and complete recovery of PB counts consistent with sustained CR.

Eleven months after initiating combination treatment, another PB NGS sample analyzed by Genoptix did not identify *MAP2K2, RUNX1, CALR*, or *ZMYM3* alterations. Instead, a benign *PDGFRB T88I* (MAF, 47%) alteration and *TET2 H1380Y* (MAF, 5%) and *DNMT3A R882S* (MAF, 15%) mutations were identified (Fig 1; Data Supplement).

Subsequently, a donor PB sample was analyzed by a Clinical Laboratory Improvement Amendments-certified Moffitt 54-gene–targeted myeloid NGS panel with an average coverage of 11,987 reads. The Moffitt NGS panel revealed a *DNMT3A R882S* mutation (MAF, 5.4%; Data Supplement). A benign *ASXL1 G652S* variant was detected in the patient and the related donor (MAF, 49%), likely reflecting a heterozygous germline variant detected in both persons as a result of shared inheritance. The *DNMT3A R882S* alteration is one of the most commonly mutated genes and positions observed in clonal hematopoiesis of indeterminate potential (CHIP). Observation of
this acquired mutation in the patient suggests donor-derived acquisition of a CHIP mutation.

At the time of this report, the patient was without GVHD symptoms, received a donor lymphocyte infusion (DLI) 16 months after trametinib initiation, and remains in CR 18.5 months after trametinib initiation (29.5 months after allo-SCT). The primary oncologist felt that a DLI may achieve the best long-term outcomes because there are no long-term efficacy data of trametinib plus a hypomethylating agent (HMA) in relapsed MDS after allo-SCT. The patient continues to receive treatment with trametinib and decitabine without evidence of dysplasia or relapse.

**DISCUSSION**

Protein function in the presence of MAP2K2 P298L has not been previously characterized to our knowledge. This MAP2K2 alteration is located in a proline-rich segment of the protein kinase domain, is near a MAP2K2 phosphorylation site, and has been observed previously in cancer. Additionally, per the Catalog of Somatic Mutations in Cancer, the MAP2K2 P298L alteration had been identified as somatic and pathogenic per their prediction tool. Despite not knowing the functional significance of the alteration, a clinical response was observed after the administration of trametinib and decitabine. Perhaps future studies can evaluate the functional significance of this MAP2K2 alteration.

Treatment options remain poor in patients with myeloid malignancy who relapse after allo-SCT. However, HMAs with or without DLI remain an attractive option in these heavily pretreated populations. Azacitidine was evaluated in patients with relapsed MDS/AML after allo-SCT followed by a DLI in patients whose disease did not respond to azacitidine. Overall, the major response rate was 29.3% (46 of 157 patients) with 15.3% (n = 24) achieving a CR. The 2-year OS was 12.4% and in those achieving a CR after azacitidine administration, the 2-year OS was 48.4%. Therefore, it is difficult to determine to what degree, if any, the clinical benefit observed could be attributed to trametinib, because HMAs with or without DLI have demonstrated clinical efficacy in patients with relapsed MDS after SCT transplant.

Adverse effects and their management with trametinib plus decitabine has not been previously discussed to our knowledge. Based on phase II data, trametinib was not believed to result in the infectious complications experienced in our case. Trametinib and decitabine were held to evaluate the etiology of the adverse effects of dermatitis and mucositis, for which a biopsy specimen demonstrated GVHD. When optimal management with steroids and immunosuppressants were not successful in ameliorating persistent mucositis, improvement was noted upon holding and reducing the dose of trametinib. Similar to phase II data, reversible transaminitis, not believed to be GVHD, occurred; holding and reducing the dose of trametinib resolved this issue and mitigated future transaminitis. At this time, it is not clear if combining trametinib with decitabine increases the incidence and severity of adverse events or if patients may be more susceptible to toxicity with trametinib therapy after transplantation, because many adverse events reported in this case overlap with the presentation of GVHD.

Alterations of DNMT3A are the most prevalent CHIP mutations and the low MAF observed in this patient is similar to that seen in several CHIP studies of healthy individuals. Investigators identified older donor age (> 40 years) as associated with a higher incidence of donor cell leukemia (P = .045), which is concordant with a previous study that observed a higher rate of somatic alterations of CHIP genes in older patients in whom there was an increased likelihood of a hematologic malignancy developing (hazard ratio, 11.1; 95% CI, 3.9 to 32.6). Another study reported that in 5.6% of patients, unexplained cytopenias after allo-SCT could be attributed to donor-engrafted CHIP and that donor age was higher among those with unexplained cytopenias (median age, 55 ± 30 years; P < .001). Based on the findings in the patient in this case report and on other studies, a large, prospective clinical trial screening donors older than 40 years for CHIP-associated mutations may be warranted.

We report the results of using trametinib in combination with a HMA for the management of relapsed MDS after allo-SCT in one patient. The patient remained in CR for 17 months from
the initiation of dual therapy, which is longer than any response reported for patients with RAS-mutated MDS or AML treated with trametinib monotherapy. Furthermore, this case provides support to characterize the MAP2K2 P298L alteration as activating and amenable to trametinib therapy, suggesting the incorporation of routine molecular testing in the population with refractory MDS.

DOI: https://doi.org/10.1200/PO.17.00110
Published online on ascopubs.org/journal/po on February 13, 2018.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

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Research Funding: Incyte (Inst)

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Stock and Other Ownership Interests: Abbvie
Consulting or Advisory Role: Celgene, Novartis
Speakers’ Bureau: Novartis, Alexion Pharmaceuticals
Research Funding: Incyte (Inst), Celgene (Inst), GlaxoSmithKline (Inst), Eleos (Inst), Boehringer Ingelheim (Inst)
Travel, Accommodations, Expenses: Celgene, Incyte, Alexion Pharmaceuticals, Novartis

ACKNOWLEDGMENT
We thank Howard McLeod for his insight and direction in the realm of personalized medicine, and the DeBartolo Family Personalized Medicine Institute and the Collins Charitable Foundation for providing us the opportunity to create personalized therapeutic approaches for our patient at Moffitt Cancer Center.

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