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High Dose Cytarabine, Mitoxantrone, Pegaspargase (HAM-pegA) in Combination with Dasatinib for the First-Line Treatment of Philadelphia Chromosome Positive Mixed Phenotype Acute Leukemia

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Abstract

The treatment of Mixed Phenotype Acute Leukemia (MPAL) is challenging due to the presence of disease characteristics of both myeloid and lymphoid leukemia. Regimens historically used to treat acute lymphoblastic leukemia are often used to treat MPAL, particularly for patients whose diseases also possess the Philadelphia chromosome (Ph+). Here we present a novel regimen, HAM-pegA+dasatinib, for the treatment of two patients with newly diagnosed Ph+ MPAL. This regimen is a blend of both myeloid-targeted and lymphoid-targeted chemotherapy agents, and is given as a single cycle of intensive chemotherapy followed by oral dasatinib maintenance therapy. Without proceeding to allogeneic transplant, this regimen produced durable remissions of 18 months and longer. This novel regimen offers an exciting alternative to other intensive regimens that require multiple cycles of intensive chemotherapy and allogeneic transplant in first remission.

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Introduction

Mixed Phenotype Acute Leukemia (MPAL) is an exceptionally rare form of acute leukemia involving cells that express both myeloid and lymphoid features. This high risk leukemia has inferior survival compared to patients with Acute Lymphoblastic Leukemia (ALL) or Acute Myeloid Leukemia (AML) [1]. Chromosomal abnormalities, such as t(9;22) (the Philadelphia chromosome, Ph+) and MLL rearrangements, are common [2]. Historically, patients with t(9;22) were considered to have particularly poor outcomes. With the advent of BCR/ABL-targeted Tyrosine Kinase Inhibitors (TKIs), survival rates have since improved and are now similar to patients with Ph+ ALL [3]. Still, beyond the expert opinion of including BCR/ABL-targeted TKIs, clear standard-of-care treatment strategies are lacking for MPAL with t(9;22) patients [4].

We hypothesize that combining pegaspargase with high-dose cytarabine plus an anthracycline can be useful for targeting both lymphoblastic and myeloid aspects of this disease. Here we describe two adult cases of MPAL with t(9;22) and B/myeloid immunophenotype treated with a novel hybrid induction regimen of HAM-pegA (high-dose cytarabine, mitoxantrone, and pegaspargase) plus dasatinib maintenance as first-line therapy.

Case Series

Case 1

A 57-year-old Caucasian woman was incidentally found to have mild leukocytosis with peripheral circulating blasts. Presenting Complete Blood Count (CBC) showed White Blood Cell (WBC) count of 14,900/μL with 23% neutrophils and 27% blasts, hemoglobin of 11.1 g/dL, and platelet count of 83,000/μL. Bone marrow core biopsy showed a hypercellular marrow (cellularity 100%) with 64% blasts. Two distinct cell lineages were identified (Table 1). The t(9;22) mutation was identified by FISH in 87.5% of cells and BCR-ABL1 (IS) was 40.7% in peripheral blood. Other cytogenetic abnormalities seen in a majority of the Ph+ cells (84.2%) included inv(2) and rearrangement of 19q. She was diagnosed with MPAL, B/myeloid with t(9;22). Cerebral spinal fluid was negative for leukemic involvement. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0, and Charlson Comorbidity Index (CCI) was 3 prior to her leukemia diagnosis.

Table 1: Cell lineage markers.

	Cell Lineage #1	Cell Lineage #2
Case 1:	CD19	CD19
	CD38	CD38
	CD34	CD34
	CD10	-
	CD22	CD22
	TdT	-
	CD33	CD33
	CD13	CD13
	-	CD11b & 11c
	-	MPO (small subset)
	-	HLA-DR
Case 2:	CD34	CD34
	CD19	CD19
	CD20	CD20
	CD22	CD22
	CD79a	CD79a
	CD10	CD10
	TdT	TdT
	CD13	CD13
	CD33	CD33
	CD38	CD38
	CD56	CD56
	-	CD11c (small subset)
	-	MPO (small subset)

Table 1 describes the two distinct cell lineages present in each patient case

The patient underwent induction with HAM-pegA plus dasatinib. This regimen consisted of cytarabine 3000 mg/m^2 Intravenously (IV) over 3 h every 12 h for 5 doses, mitoxantrone 6 mg/m^2 IV over 1 h immediately following cytarabine dose number 1, 3, and 5, and pegaspargase 3750 units (capped dose) IV over 2 h on day 4. Additionally, dasatinib 100 mg daily began day 1 and was given continuously.

The patient was hospitalized for an additional 36 days. Induction chemotherapy was complicated by febrile neutropenia, sepsis, type 2 Non-ST-Elevated Myocardial Infarction (NSTEMI), and transient hepatotoxicity. The febrile neutropenia and sepsis episode occurred on day 13 secondary to *Streptococcus agalactiae* and *Eschericia coli* bacteremia, and the NSTEMI was believed to be secondary to this sepsis event. The hepatotoxicity was characterized by grade 3 liver function test abnormalities, peaking between days 21 and 32. This improved with levocarnitine and vitamin B supplementation and eventually recovered to baseline.

Her neutrophils and platelets recovered on day 20 and 23, respectively. A day 25 bone marrow aspirate showed blasts of <5% and FISH was negative for t(9;22), confirming complete hematologic and cytogenetic response. BCR-ABL1 (IS) significantly decreased to 0.6%. Unfortunately, the patient was lost to follow-up immediately following discharge and did not proceed to transplant. It is assumed that her dasatinib was discontinued during this time. She presented again to our hospital after 17.7 months in remission, now with relapsed disease for which she was started on blinatumomab plus imatinib [5]. Imatinib was discontinued during cycle 2 due to toxicity, and was eventually switched to bosutinib. At the time of this writing, she is doing well nearly 27 months since the initiation of HAM-pegA for initial induction, and she remains in her second complete remission.

Case 2

A 22-year-old African-American man presented with diffuse pain, easy bruising, bleeding gums, and weight loss. CBC on admission was remarkable for platelets of 76,000/μL and hemoglobin of 11.3 g/dL, but was normal for WBC (6,100/μL) and neutrophils (21%). His bone marrow core biopsy was hypercellular (cellularity 100%) with 88% blasts. Two distinct cell lineages were identified (Table 1). A complex karyotype was seen, which included hyperdiploidy (gain of chromosomes 5, 8, 21, derivative of 22, and a marker chromosome) as well as t(1;5). Additionally, FISH identified t(9;22) in 93% of cells, gain of AML1 in 35% cells, and a CRLF2 rearrangement in 43% of cells. BCR-ABL1 (IS) was 0.2% in peripheral blood. He was diagnosed with MPAL, B/myeloid with t(9;22). There was no evidence of central nervous system disease. Both his ECOG performance status and CCI were 0 at the time of his leukemia diagnosis. He underwent induction with HAM-pegA plus dasatinib. He additionally received a single dose of rituximab 375 mg/m^2 IV on day 5 of induction.

This patient remained hospitalized for an additional 28 days. His course was complicated by bleeding at his catheter site, as well as infectious complications including pseudomonas bacteremia, presumptive herpes simplex virus reactivation, and cellulitis of the foot. No other toxicities were experienced.

Full count recovery occurred on day 18 for neutrophils and 19 for platelets. A bone marrow biopsy was performed on day 26 which showed <5% blasts and a normal karyotype confirming complete hematologic and cytogenetic response. Additionally, BCR-ABL1 (IS) was undetectable confirming complete molecular response. The patient was not amenable to any further consolidation chemotherapy or hematopoietic stem cell transplant, and instead remained on dasatinib maintenance. The patient had a durable remission of 25 months, before relapsing with predominantly pre-B-ALL immunophenotype and negative myeloid markers. CD20 and BCR-ABL1 positivity remained, and he was subsequently initiated on R-Hyper CVAD plus ponatinib.

Discussion

The overall treatment approach to a newly diagnosed MPAL patient often includes induction chemotherapy followed by allogeneic hematopoietic stem cell transplant once remission is achieved [1]. However, a myriad of induction chemotherapy regimens have been tried, some of which are based on AML regimens, others based on ALL regimens, and some of which are a hybrid of the two. Expert opinion has largely preferred age-appropriate ALL-based regimens in the absence of well-designed prospective studies [6]. In a recent meta-analysis, ALL-based regimens were more likely to achieve complete remission as compared to AML-based regimens (OR=0.33, 95% CI 0.18 to 0.58), and had similar rates of complete remission as hybrid regimens [7]. Presumably, the higher sensitivity to ALL regimens may be in part due to MPAL cells originating from more primitive and quiescent leukemia-initiating cells that are not as rapidly dividing. This may render them less sensitive to infusional cytarabine-based regimens (i.e. myeloid regimens) that are S-phase dependent.

In a report evaluating the use of hyper-CVAD, a primarily ALL-based regimen, in the first-line treatment of MPAL patients,

excellent outcomes were seen [8]. Hyper-CVAD achieved a high overall response rate (86%), a high rate of allogeneic transplant (63% of responders), and an excellent overall survival (median overall survival not yet reached with a median follow-up time of 37 months) in this patient population [8]. However, hyper-CVAD followed by allogeneic transplant is still limited by its intensity of chemotherapy, requiring multiple cycles of chemotherapy associated with a high rate of neutropenic fever and other complications.

Our treatment approach does not meet the strict definition of a hybrid regimen as defined in by Maruffi et al. which was defined as including steroids, vincristine, asparaginase, cytarabine and anthracycline. Still, the principles of combining components of a historically AML-based regimen (cytarabine and mitoxantrone) with components of a historically ALL-based regimen (asparaginase) exhibits the same principle of a "hybrid" regimen, and makes conceptual sense in treating patients with distinct features of both disease states.

Our institution has had success with using the HAM-pegA backbone in patients with relapsed AML, which was the first report of this regimen using the pegylated version of asparaginase [4]. The addition of dasatinib to HAM-pegA has not been previously studied, however research has found promising outcomes when BCR-ABL-targeted TKIs are combined with chemotherapy, compared to chemotherapy alone [9]. Few case reports exists utilizing dasatinib in this setting [10]. Still, by extrapolating from ALL literature, it offers a promising choice of TKI in upfront therapy [11].

Despite not receiving hematopoietic stem cell transplant in first remission, both of our patients experienced durable remissions. In the first case, the patient had a significant gap in her dasatinib therapy due to being lost to follow-up, yet she still achieved nearly an 18-month remission. In the second case, where dasatinib was continued and adherence confirmed, the patient achieved a first remission of over 2 years. These cases suggest that modern BCR/ABL-targeted TKI therapy may be sufficient in maintaining remission after a single course of induction therapy in patients with Ph+ MPAL. This is an exciting feature of HAM-pegA plus dasatinib, in that it produced durable remissions with only one cycle of intensive chemotherapy followed by maintenance oral TKI therapy without proceeding to allogeneic transplant. This significantly reduces the risk of toxicity by foregoing multiple cycles of intensive chemotherapy, which other regimens such as hyper-CVAD may be limited by. For medically fit young adults and adults, HAM-pegA plus dasatinib may be a valid alternative to hyper-CVAD-based regimens in patients with Ph+ MPAL. There also may be opportunity to delay transplant to first relapse. Further research is needed to understand which patients may benefit most from this type of treatment strategy.

Conclusion

The rarity of MPAL, in addition to frequent exclusion from clinical trials, makes it challenging for a standard of care therapy to be established for these patients. For two patients with newly diagnosed MPAL with t(9;22), HAM-pegA plus dasatinib, a regimen consisting of a single course of induction chemotherapy followed by maintenance dasatinib, achieved remissions of 18 months or longer.

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