CONFLICT OF INTEREST

Nothing to report

AUTHOR’S CONTRIBUTIONS

All authors read and approved the final version of the manuscript. D.F. performed gene mapping experiments, organized micro-CT scans, genotyped and characterized the MPP1/p55 null mice, and wrote the first draft of the article. T.H. regenerated the MPP1/p55 null mice and performed immunoblotting of MPP1 protein. Y.L. performed erythrocyte osmotic hemolysis assays, helped with the regeneration of MPP1/p55 null mice, and gel electrophoresis experiments. M.J. identified the patient, performed clinical evaluation and initial genetic testing, supplied the patient-derived material, and edited the article. A.C. supervised the project, organized the figures, and wrote multiple drafts of the article as principal investigator.

ORCID

Athar H. Chishti https://orcid.org/0000-0003-0335-1861

REFERENCES


SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

DOI: 10.1002/ajh.25332

Outcome and impact of post-remission strategy after MIDAM regimen in patients with relapsing or refractory acute myeloid leukemia

To the Editor:

Patients with relapsed or refractory acute myeloid leukemia (R/R AML) have very poor outcomes, and the management of such situations remains an acute challenge.1 Combining gemtuzumab
ozogamicin (GO), intermediate-dose Ara-c, and mitoxantrone (MIDAM) has been suggested as a valid salvage therapy option based on a prospective phase II study. However, more extensive data on such an approach are needed to determine and improve the optimal use of this regimen.

All consecutive patients with R/R AML treated with the MIDAM regimen in our center (Clermont-Ferrand University Hospital) between 2008 and 2013 were included in our study. Karyotyping was performed for all patients, and the mutational statuses of NPM1, FLT3, and CEBPA were assessed in cases of normal karyotype AML, as previously reported. Risk assessment was evaluated according to the European Leukemia Net (ELN) guidelines 2010. CD33 expression was assessed by flow cytometry.

The MIDAM regimen consisted of GO 9 mg/m² on day 4, cytarabine 1 g/m² every 12 hr on days 1 through 5, and mitoxantrone 12 mg/m²/day on days 1 through 3.

Patients with CR or CRp after MIDAM underwent postremission therapy. Allo-HSCT was performed in patients with available related or unrelated donors (HLA-matched or HLA-mismatched) and an appropriate fit (hematopoietic cell transplantation-specific comorbidity index [HCT-CI] <3, age <70 years). In cases where no donor was available, chemotherapy alone or autologous transplantation was proposed.

MIDAM-related safety was registered within 45 days after the start of induction therapy. Allo-HSCT was performed in patients with available related or unrelated donors (HLA-matched or HLA-mismatched) and an appropriate fit (hematopoietic cell transplantation-specific comorbidity index [HCT-CI] <3, age <70 years). In cases where no donor was available, chemotherapy alone or autologous transplantation was proposed.

A total of 86 consecutive patients with relapsed (n = 62) or refractory (n = 24) AML were included. Median age was 60 years (range, 17-75). The MIDAM regimen was administered as salvage therapy after 1 (n = 73) or more (n = 13) therapeutic lines. Distribution according to ELN 2010 cytogenetic/molecular risk classification was as follows: favorable (n = 12), intermediate-1 (n = 23), intermediate-2 (n = 15), high risk (n = 22), and not available for 13 patients.

Infusion-related reactions attributed to GO were observed in 24 (28%) patients, and tumor lysis syndrome was seen in 4 (4.6%) patients. Grade 3-4 hyperbilirubinemia was observed in 11 patients (12.8%), and grade 3 to 4 febrile neutropenia was observed in all the patients. Forty-six (53.5%) patients had persistent thrombocytopenia at day 45. Eight (9.3%) patients had veno-occlusive disease (VOD); all cases of reported VOD were associated with MIDAM induction rather than allo-HSCT. A total of nine (10%) deaths during the induction phase (within 30 days after the start of the MIDAM regimen) occurred. Four cases of death were related to sepsis, 2 cases to VOD, 2 cases to acute respiratory distress, and 1 to pneumonia. Deaths during the induction phase were significantly more frequent among those with poor performance status (33% if ECOG >1% vs 6% if ECOG was 0 or 1, P = .007). No significant influence of age (<60 years old vs ≥60 years old) was found.

The OR rate (ORR) was 63% (CR, 36%; CRp, 27%). ORR was significantly better in patients who had relapsed vs refractory AML (69.4% vs 45.8%, respectively; P = .039), in patients with low WBC (71% if <10 G/L vs 44% if WBC >10 G/L, P = .028) and in those with good performance status (70% if ECOG was 0 or 1 vs 27% if ECOG >1, P = .003). No significant influence of age (<60 years old vs ≥60 years old), percentage of CD33-positive cells, ELN cytogenetic/molecular risk or disease status (de novo vs secondary AML) was found.

The median follow-up was 6 years. Among the 54 patients with CR or CRp, postremission therapy consisted of chemo-based approaches in 13 patients (chemotherapy only, n = 10; chemotherapy + auto-HSCT, n = 3) and allo-HSCT in 29 patients (including 7 with consolidation chemotherapy prior to allo-HSCT). The allo-HSCT conditioning was MAC in 8 patients and RIC in 21 patients. The stem cell sources included related donors (n = 7), unrelated donors (HLA-matched in 17 patients and HLA-mismatched in 3 patients) or umbilical cord (n = 2). Twelve patients did not receive any consolidation therapy.

The 2-year RFS was 28%. No influence of age (P = .480), WBC count (P = .078), percentage of CD33-positive cells (<30% vs >30%, P = .215) or ELN risk classification group was observed for 2-year RFS. Allo-HSCT as postremission therapy conferred significantly
better 2-year RFS compared with chemo-based approaches and on consolidation therapy (51%, 33%, and 9%, respectively, P = .001) (Figure 1).

Among the whole population, the 2-year OS was 20%. High WBC count greater than 10 G/L (P = .025), intermediate- and high-risk ELN cytogenetic findings (P = .036), and ECOG performance status greater than one (P = .009) were significant adverse prognostic factors of OS, and no influence was found for age, disease status (P = .108), and percentage CD33-positive cells (P = .457) on OS. Allo-HSCT as postremission therapy was associated with improved 2-year OS (43%) compared with patients without an available donor and those treated with chemotherapy-based approaches (15%) (P = .005) (Figure 1). Importantly, none of the patients treated with allo-HSCT had VOD. Of note, no patient with VOD after MIDAM induction therapy received allo-HSCT.

Cause of death was related to AML in 62% of cases. For the remaining cases, 18% were related to sepsis, 7% to hemorrhagic complications and 13% to other causes, including graft versus host disease (GVHD) in 2 patients, VOD in 2 patients (related to MIDAM induction rather than allo-HSCT), pneumonia in 2 patients, cardiac arrhythmia in 1 patient, and pulmonary embolism in 1 patient.

The MIDAM regimen is a valid option for achieving CR in patients with R/R AML.2 This study aimed to investigate the efficacy and tolerability of this approach in an extended cohort and to analyze the impact of postremission therapy.

We analyzed data from 86 patients with relapsed or refractory AML, which represents the largest series of patients treated with this protocol thus far. The CR rate was 63%, which was in line with the results of a previous phase 2 trial.2 Disease status before induction of the MIDAM regimen plays an important role in the response to salvage therapy. Indeed, the CR rate was found to be improved in patients with relapsed compared with refractory disease, likely due to the increased incidence of genetic alterations and multidrug resistance phenotype associated with refractory AML. Conversely, no impact of molecular cytogenetic abnormalities was found on response rate, in contrast to results observed in newly diagnosed AML.6

One major concern is the risk of VOD related to the use of GO, particularly for patients who undergo subsequent allo-HSCT. The use of MIDAM before allo-HSCT is thought to increase this risk.5 In our cohort, allo-HSCT in patients who achieved CR after the MIDAM regimen was well tolerated and showed an acceptable toxicity profile, and no VOD was found after an extended follow-up.

GO in fractionated doses has been shown to be highly effective in association with chemotherapy and could be an interesting option in our MIDAM regimen because this approach allows the delivery of high cumulative doses without excessive toxicity.6

In a univariate analysis related to age, this study revealed no significant difference in CR between the different age groups, and the results suggest that the MIDAM regimen could be an acceptable choice as salvage treatment in the elderly. Induction-related death was linked to performance status, with no significant influence of age.

In conclusion, the MIDAM regimen in R/R AML is a viable therapeutic option as salvage chemotherapy and is associated with an acceptable toxicity profile. Allogeneic transplantation is the consolidation of choice and can be performed safely after MIDAM with no increased risk of VOD.

CONFLICT OF INTEREST
Nothing to report.

ORCID
Salem Bahashwan https://orcid.org/0000-0002-5635-230X
Marc G. Berger https://orcid.org/0000-0003-1858-0587

Salem Bahashwan1,2 Cécile Moluçon-Chabrot1,2 Eric Hermet1,2 Aurélie Ravinet1,2 Aurore Douge1,2 Lauren Veronese1,3 André Tchirkov1,3 Richard Lemaî1,2 Marc G. Berger1,4 Richard Veyrat-Masson1,4 Olivier Tournilhac1,2 Jacques-Olivier Bay1,2 Romain Guièze1,2

1Clermont Auvergne University, Clermont-Ferrand, France
2Unit of Adult Cell Therapy and Clinical Hematology, University Hospital of Clermont-Ferrand, Clermont-Ferrand, France
3Cytogenetic Laboratory, University Hospital of Clermont-Ferrand, Clermont-Ferrand, France
4Department of Biology, University Hospital of Clermont-Ferrand, Clermont-Ferrand, France

Correspondence Romain Guièze, Service d’Hématologie Clinique Adulte et de Thérapie Cellulaire, CHU Estaimbourg, 1 place Lucie et Raymond Aubrac, Clermont-Ferrand 63003, France. Email: rguiize@chu-clermontferrand.fr

REFERENCES
Single-agent venetoclax induces MRD-negative response in relapsed primary plasma cell leukemia with t(11;14)

To the Editor:
Plasma cell leukemia (PCL) is the most aggressive form of plasma cell dyscrasia. It is characterized by the presence of more than 20% and/or more than 2 × 10^9/L of circulating plasma cells (PCs). Primary plasma cell leukemia (pPCL) that presents de novo should be distinguished from secondary PCL, which corresponds to the leukemic transformation of pre-existing multiple myeloma (MM). Primary PCL is characterized by an increased frequency of adverse laboratory and clinical features as well as higher genetic instability than MM. Despite the introduction of novel agents into clinical practice, the prognosis of pPCL remains poor, with an estimated overall survival of 1-2 years in elderly patients and about 3 years in younger patients eligible for stem cell transplantation (SCT).1,2

Venetoclax is a potent, highly selective Bcl-2 inhibitor, representative of the so-called BH3 mimetics. This novel group of agents targets the anti-apoptotic proteins, thus inducing tumor cell death. It has been demonstrated in vitro as well as in vivo that a subgroup of PCs is Bcl-2 dependent, and thus sensitive to venetoclax. This subset is restricted to those harboring t(11;14).3,4 While translocation t(11;14) is only present in approximately 15-20% of MM patients, it is reported in up to 50% of pPCL patients, making venetoclax a very promising drug for such an aggressive disease.2

A 58-year-old man with life-threatening acute renal failure (creatinine: 504 μmol/L; urea: 32.4 mmol/L, hyperkalemia of 6.4 mmol/L, and hypercalcemia of 3.45 mmol/L) was admitted to our intensive care unit in May 2017. The patient’s blood count showed leukocytosis of 30.7 × 10^9/L with 35% of circulating PCs (Figure 1A) and anemia with hemoglobin level of 93 g/L. Bone marrow (BM) biopsy revealed 57% infiltration of lambda clonal PCs confirmed by flow cytometry. The paraprotein IgG lambda level was 8.9 g/L and the concentration of lambda free light chains (FLC) was 2348 mg/L with a pathological FLC ratio of 2134. Fluorescence in situ hybridization analysis revealed the presence of translocation t(11;14)(q13;q32) and subsequent translocation t(9;14)(p13;q32) (Figure 1B,C). A low dose CT (ldCT) scan demonstrated multiple osteolytic skeletal lesions. The diagnosis of pPCL was established based on these results and treatment with bortezomib and dexamethasone (VD) was immediately initiated. The treatment was intensified after 2 cycles with additional 2 cycles of hyperCVAD-VD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone). The patient’s renal functions completely normalized after induction therapy and he subsequently underwent ASCT with a reduced dose of melphalan 140 mg/m² in September 2017. This procedure was complicated by symptomatic dilated cardiomyopathy with a drop in left ventricle ejection fraction to 38% (EF of 65% atbaseline). The hematological response after front-line therapy was very good partial response (VGPR) with the normalization of FLC ratio and persistent positive serum immunofixation.

Due to the highly aggressive nature of pPCL, our patient was frequently followed-up. The first signs of relapse occurred in February 2018; 6 months after high dose therapy. The elevation of FLC lambda was accompanied by the deterioration of renal functions with rapidly increasing levels of serum creatinine. BM was infiltrated by 2% of PCs with 100% being lambda clonal. FDG-PET/CT demonstrated obvious progression compared with ldCT performed at the time of diagnosis. In the Czech Republic there is limited access to novel agents for treatment of pPCL. We took into account the fact that the patient harbors translocation t(11;14) and requested venetoclax free of charge from Abbvie as part of the pre-approval access program. Venetoclax as a single agent was administered orally once daily at the dose of 1200 mg in 21-day cycles. Venetoclax induced a very rapid decrease in FLC lambda levels, translating into the normalization of FLC ratio after the first cycle (Figure 1D). Treatment response was evaluated after 9 cycles of single-agent venetoclax. We performed next generation flow cytometry (NGF) for the evaluation of minimal residual disease (MRD) within BM according to EuroFlow recommendations. We confirmed flow MRD-negative response with a sensitivity level of 10^-6 (Figure 1E,F). Moreover, we did FDG-PET/CT that demonstrated the disappearance of all previously reported pathological lesions (Figure 1G,H). The treatment has been well tolerated, no drug related serious adverse events have been observed and the only toxicity has been grade 1 thrombocytopenia. At the moment (October 2018) our patient is still receiving venetoclax monotherapy with no new safety signals.

Primary PCL is one of the most aggressive blood cancers and the therapeutic outcomes of relapsed pPCL patients ineligible for SCT are especially poor. Our patient was not able to undergo SCT because of his cardiac co-morbidities, thus the treatment options remained very limited. Translocation t(11;14) is a routinely investigated cytogenetic abnormality that serves as a useful biomarker predicting sensitivity to venetoclax. This molecular subset is associated with high Bcl-2, and low Bcl-XL and Mcl-1 mRNA expression, resulting in higher sensitivity to Bcl-2 inhibition. In our case we also performed expression profiling of the anti-apoptotic proteins Bcl-1, Bcl-XL, and Mcl-1 to predict the sensitivity to venetoclax in vitro.5 We determined Bcl-2/Bcl-Xl and Bcl-2/Mcl-1 mRNA ratio using quantitative polymerase chain reaction on FACS sorted PCs. The mRNA ratio of Bcl-2/Bcl-