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Letter to the Editor

The feasibility of venetoclax and decitabine in therapy-related acute myeloid leukemia with concurrent advanced non-hematological malignancies

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To the Editor

Therapy-related acute myeloid leukemia (t-AML) is an uncommon complication of cytotoxic therapies administered for unrelated malignancies [1]. The entity is associated with poor outcomes as the result of low response rate as well as excessive treatment-related morbidity and mortality when intensive induction regimens are utilized [2–5]. Therapy-related AML is enriched with adverse cytogenetics [complex/monosomal karyotype, *KM2TA* (*MLL*) rearrangements] as well as high-risk molecular mutations (*TP53*) that confer resistance towards conventional chemotherapy [4,6,7]. Management of t-AML in the context of active advanced non-hematological malignancies is even more challenging. This scenario is perceived as a terminal condition with very limited therapeutic options considering the usual decline in patient performance status concurrent with AML diagnosis, residual toxicities that the patient carries from previous cytotoxic therapies, as well as the fact that an incurable advanced malignancy predates the AML. Hypomethylating agents (HMAs) have been offered as a low intensity treatment in these cases with the goal of prolonging survival, however, published data addressing their benefit in this situation are lacking. Furthermore, response to single agent HMA is disappointing in AML overall [8], and their impact on the non-hematological malignancy progression is trivial if any.

Venetoclax is a selective BCL-2 inhibitor which when combined with HMA (VEN-HMA), has remarkable activity in newly diagnosed AML, including patients who are older or deemed unfit for conventional chemotherapy [9]. Encouraging activity of VEN-HMA was also observed in relapsed/refractory (r/r) AML as well [10]. The combination is well-tolerated and associated with low treatment-related mortality (TRM), even in frail patients [9]. Herein, we describe our experience in patients with active advanced non-hematological malignancies who develop t-AML and were treated with VEN-HMA.

We retrospectively reviewed all AML patients treated at City of Hope between June 2016 and April 2019, and identified 8 patients with t-AML and active advanced non-hematological malignancies who received VEN-HMA. Their median age was 61 years (range: 54–81) and 4 (50%) were male. All patients had active and recurrent stage IV non-hematological malignancies, including ovarian, breast, malignant paraganglioma, lung, sarcoma and pancreatic. Leukemia genetics showed complex karyotype in 2, *KM2TA* gene rearrangement in 2, 7q deletion or monosomy 7 in 4, and *TP53* mutation in 2 patients. All patients were treated with VEN-HMA for newly diagnosed AML except for one who was treated with the combination for r/r AML after failing 2 prior AML therapies. All patients had decitabine as HMA, and 4 (50%) of them received first cycle as 10-days schedule (Table 1).

Six (75%) patients achieved complete remission (CR)/CR with incomplete count recovery (CRi), including 5 with newly diagnosed AML and 1 with r/r AML. The median number of venetoclax and decitabine cycles administered was 3 (1–8). None of the treated patients suffered death within eight weeks from initiating VEN-HMA. Two of the responders eventually relapsed, and 3 died in remission. Causes of death for the entire cohort were relapsed AML in 2 patients and sepsis in 4 other patients. Five patients received concurrent treatment for the underlying non-hematological malignancies, including hormonal therapies, immunotherapy, tyrosine kinase inhibitor and chemotherapy (Table 1).

We describe our limited experience of administering VEN-HMA in patients with t-AML and concurrent advanced non-hematological malignancy. The combination appears feasible and well-tolerated in this population, even when combined with other antineoplastic therapies for the underlying non-hematological malignancy. Early treatment-related mortality in this setting was low and appears comparable to VEN-HMA data when administered in frontline setting in patients without active malignancies [9]. Furthermore, the response rate was high and encouraging in our cohort with active advanced non-hematological malignancies, and the majority of patients achieved CR/CRi. Some patients were able to receive up to 8 cycles of VEN-HMA, and 2 patients survived a year after their initial t-AML diagnosis while they were on the combination therapy.

Prevalence of AML with concurrent advanced non-hematological malignancies is expected to rise in the future given the availability of effective therapies in the recent years, which led to prolong survival of affected patients with advanced stage malignancies past the latency period required for t-AML to develop [11,12]. Induction with idarubicin-cytarabine (7 + 3) regimen or liposomal daunorubicin/cytarabine (Vyxeos) are not appealing choices for t-AML patients with

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Table 1
Patients characteristics, therapy and outcomes.

N	Age	Sex	NH cancer	Stage & setting	AML setting	Cytogenetics	Molecular profile by NGS	VEN/HMA cycles	Best response	Concurrent therapy	NH malignancy response	Relapse	Months from start therapy until last f/u	Outcome
1	59	F	Ovarian	Recurrent, stage IV	Untreated	43-45,XX,-3,-5,-7, +8,-17, add(22)(q13)	Negative	8	CR	Nivolumamb + gemecitabine, and then Taxol	Stable, and then progression	Yes	12	Death
2	59	F	Breast	Recurrent, stage IV	Untreated	46,XX,t(9;11)(p21;q23)	*ASXL1, FLT3-TKD, UBR5, KMT2A-MLLT3*	2	CRi	Letrozole	Response by markers	No	2.5	Death
3	54	F	Ovarian	Recurrent, stage IV	r/r	46,XX,del(7)(q32q34),inv(16)(p13)	*ND*	1	CRi	Debulking surgery	Markers stable	Yes	12.5	Death
4	56	M	Malignant paraganglioma	Recurrent, stage IV	Untreated	45,XY,-7	*RUNX1, KRAS*	2	CR	None (low grade)	No evaluation	No	5	Death
5	81	F	Breast	Recurrent, stage IV	Untreated	43~44,XX,ins(1)(p36.1;q32q42),-3,del(5)(q13q33),der(6)t(3;6)(q12;p25),der(6;12)(q10;q10),-7,-18	*TP53*	6	CRi	Letrozole	Response	No	8.5	Death
6	62	M	Lung	Multifocal, advanced	Untreated	46,XY	*DNMT3A, WT1, NPM1*	7	Refractory	Osimertinib	Stable	NA	9.5	Death
7	71	M	High grade leiomosarcoma	Refractor, stage IV	Untreated	46,XY,t(9;11)(q21;q23)	ND	3	Refractory	None	Progression	NA	3.5	Alive
8	65	M	Pancreatic VIPoma	Recurrent, stage IV	untreated	ND	*TP53*	3	CRi	Lanreotide	No evaluation	No	3	Alive

N: number; NH: Non-hematological; NGS: next generation sequencing; VEN: venetoclax; HMA: hypomethylating agent; CR: complete remission; CRi: CR with incomplete remission; ND: not done.

concurrent advanced malignancies as the risk of such regimens markedly outweighs the benefit. Toxicities for these regimens are excessive in someone with incurable second malignancy often with prior anthracycline exposure, and moreover, the expected response rate is low due to the fact that t-AML frequently carries high-risk genetics such as *TP53* mutation and complex karyotype that confer resistance to conventional chemotherapies [13]. Therefore, a regimen such as VEN-HMA represents a promising advance for management of these patients given its excellent tolerability and high response rate even with high-risk genetics. VEN-HMA could provide a backbone to with other agents could be added to treat both the t-AML as well as the concurrent non-hematological malignancy.

Our case series is retrospective and small, and there is very likely a selection bias in which only reasonably fit patients were offered such induction while others who had very poor performance status were not considered candidates for any therapy. Although CR rate is encouraging, it is also difficult to determine the actual survival benefit that VEN-HMA therapy provides, since patients with adverse genetics tend to have lower survival rates with VEN-HMA [9], and will inevitably relapse without consolidative therapy such as allogeneic hematopoietic stem cell transplantation for which these patients with concurrent active malignancies are not eligible for.

Although t-AML with another concurrent malignancy has traditionally been an exclusion criteria for AML trials, this policy should be reevaluated in future trials of active and well tolerated regimens such as VEN-HMA since a subset of such patients may derive survival benefit. Death in CR from sepsis related to neutropenia is a concern for patients treated with VEN-HMA and this may be particularly true for patients with concurrent malignancies who may have poor bone marrow reserve to begin with. All of these factors notwithstanding, our results are encouraging and this combination should be at least considered an option to treat patients with AML and active non-hematological malignancy, at least for those in whom the non-hematologic cancer is under reasonable control.

Declaration of Competing Interest

GM is on the speakers' bureau for Abbvie; VP has served on the advisory boards for Abbvie; all other authors declaring no competing financial interests.

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