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An intensive approach to treatment for older patients with relapsed isolated NPM1 mutated AML

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ABSTRACT

We present a short case series of elderly patients with NK-AML and isolated NPM1 mutation who were treated with intensive chemotherapy, achieving significant CRs multiple times on reinduction, even with a single course.We hope to highlight the NPM1 as a molecular marker in elderly for consideration of aggressive treatment, even if abridged, as this subset may achieve a durable, good quality responses at diagnosis or subsequent relapses.

We report our experience in treating elderly but fit individuals with AML and NPM1 mutation. We would particularly like to highlight the ability to re-induce remission repeatedly on subsequent relapses with the possibility of achieving a durable response with only a single course of re-induction treatment. Older AML patients who relapse are generally not offered intensive salvage treatments but we report a subgroup with clinically meaningful response to such intervention.

We present 3 cases of older patients with AML with isolated NPM1 mutation treated repeatedly with intensive chemotherapy.

Case 1 was a 75-year-old female diagnosed with normal karyotype (NK) AML with isolated NPM1 mutation on a background of longstanding chronic neutropenia. She was treated with intensive therapy in the NCRI AML16 clinical trial (Table 1). She had a morphological CR1 for around 16 months. First relapse was successfully treated with a single course of intensive relapse treatment (Table 1) to achieve a dysplastic CR2 for 12 months. At 2nd relapse, she had acquired FLT3 ITD in addition to NPM1 mutation but achieved CR3i for 10 months and a CR4 lasting for 10 months with single courses of intensive treatments (Table 1). Unfortunately, she died during re-induction at 4th relapse with an encephalopathic illness and cavitating pulmonary infection.

Case 2 was a 70-year-old male with relapsed NK-AML, and NPM1 mutation identified at first relapse. He was originally treated for NK AML (FAB-M6) in NCRI AML14 (Table 1)and achieved CR1 for 7 years. Diagnostic samples at initial presentation were not available to confirm the NPM1 status but we feel this episode was unlikely to be therapy related since t-AML with isolated NPM1 is rare and we can reasonably assume NPM1 mutation at diagnosis given that NPM1 is normally stable at relapse. He received re-induction with two courses of ADE+ATRA (Table 1) and achieved CR2i (with mild thrombocytopenia) of 16 months duration. Simultaneous with his 2nd relapse (molecularly stable) he was also diagnosed with locally advanced prostate carcinoma. He received one re-induction course of FLAG chemotherapy as this was complicated by prolonged hospitalisation for sepsis and cachexia and had a CR3 duration of 7 months.The 3rd relapse was treated successfully into CR4 again with a single course of FLAG but lasted 4 months. The patient was deemed unsuitable for further re-induction at 4th relapse.

Case 3 was a 69-year-old fit man with NK-AML and isolated NPM1 mutation treated in the NCRI AML 16 trial (Table 1). CR1 duration was 18 months with self-reported very good QoL. At first relapse (molecularly stable) he was re-induced with 1 course of ADE (10+3+5) followed by 2 courses of consolidation with cytarabine [3 gm/m^2]. CR2 was maintained for 39 months until a 3rdrelapse, which was successfully treated with a single course of FLAG. He developed locally advanced carcinoma prostate, treated with hormone manipulation in CR2. His CR3 is ongoing for over 12 months.

Case 1 and 2 had four relapses with an OS of 5 years and 11 years from the first diagnosis of AML. Three relapses were successfully managed to achieve remission and it is worth noting that Case 1 achieved this thrice and case 2 twice with a single course of intensive re-induction. The average CR duration was 11.5 months and 22.75 months respectively. Both had a very good self-reported quality of life (QoL) in between relapses. Case 3 had a significant CR2 for over 3 years and responded well to reinduction with a single course of FLAG and remains in CR3, with a very good self-reported

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Table 1
Summary of the cases-elderly AML with NPM1 mutation as sole abnormality.

	Case 1	Case 2	Case 3
Age at diagnosis	75 years female	63 years male	69 year male
Comorbid illnesses	None	none	Frozen shoulder
Induction treatment	DA 3+10, 3+8, 2+5 As per AML16 trial 1 cycle of azacitidine maintenance	DAT 3+10, 3+8 – MIDAC ICE 2+3	DCLo+1 course of Mylotarg As per AML16
Duration of CR1	16(18 if include 2 months of observation) months	100 months	18 months
2nd treatment	ADE+ATRA 1 course	ADE+ATRA 2 courses	ADE+intermediate dose Ara C
Duration of CR2	12 months	18 months	39 months
3rd treatment	FLAG	FLAG	FLAG
Duration of CR3	10 months	7 months	Ongoing
Treatment	Mercaptopurine ADE	FLAG	
Duration of CR4	10 months	7 months	
Cause of death	Died in 4th relapse	Died in 4th relapse	NA
OS from diagnosis	5 years	11 years	Alive in CR3
Total relapses	4	4	2
Average CR duration	11.5 months	27.75 months	28.5 months

DA	Daunorubicin+Cytarabine
DClo	Daunorubicin+Clofarabine
ADE	Daunorubicin+Cytarabine+Etoposide(ADE)
MIDAC	Modified Intermediate-Dose Cytarabine
FLAG	Fludarabine, Cytarabine, GCSF
ICE	Idarubicin , high-dose Cytarabine (HiDAC), Etoposide

QoL. Even the emergence of FLT3 ITD (which was always assessed for all the patients at each relapse) in case 1 did not induce chemoresistance with a further 20 months of CR achieved beyond the acquisition of FLT3 ITD.

Limitations in our cases series include:

(1) The lack of NPM1 mutation analysis at all relapses as it was not local protocol but when tested on subsequent relapses, NPM1 has been found to be mutated on multiple occasions, implying that it was likely to be the same clone.We have information regarding the NPM1 mutation status at various time points for each patient as demonstrated in Table 2.
(2) Lack of objective assessment of QoL, which is because of the retrospective nature of case compilation.

The role of intensive treatment is established only in selected elderly AML patients [1–3] and only a minority of such patients would be deemed suitable, mostly due to constraints from poor chemotherapy tolerance in view of age and comorbid illnesses.

NPM1 mutation is present in a similar proportion of younger and elderly (>60 years) AML patients (52.1 vs. 66.4% of NK AML) [4]. It is an independent predictor of better survival and longer duration of remission in multivariate analyses when the FLT3 was wild type at diagnosis [4,5]. A multivariate analysis in AML-NK patients ≥ 70 years found NPM1 mutation as the sole independent parameter influencing prognosis [6].

It has been proven that NPM1 mutated AMLs are highly responsive to chemotherapy in patients under 60 years [7–10]. In ≥ 60 years with NPM1 mutation, following treatment with intensive protocols, CR rates were higher (84% vs. 48%) and the relapse free survival (23% vs. 10% at 3 years) and OS (35% vs. 8% at 3 years) were better [6] in comparison to unmutated NPM1. The independent prognostic impact was most pronounced in ≥ 70 years [6]. Intensive treatment of the fit octogenarian population also results in significantly longer overall survival in patients with NPM1 mutation as a sole abnormality while FLT3 ITD did not have any effect [11]. These studies suggest that NPM1 mutation may be used as a molecular marker in elderly patients for consideration of aggressive treatment.

Table 2
Summary of the NPM1 mutation status at various time points.

	Case 1	Case 2	Case 3
Diagnosis	Mutated	Not known	Mutated
CR1	Not known	Not known	Not known
1st relapse	mutated	Mutated	Not known
CR2	Not known	Not known	Not known
2nd relapse	Failed npm1 but flt3+	Not known	Mutated
CR3	Mutated	Not known	Not known
3rd relapse	Mutated	Mutated	Not applicable
CR4	Not known	Not known	Not applicable
4th relapse	Mutated	Not known	Not applicable

Thus, we wish to reiterate the favourable impact of NPM1 mutation on prognosis and chemosensitivity in elderly patients, and to draw attention to the following:

(a) This subset of AML patients may attain a durable, good quality response with a single cycle of intensive therapy
(b) They could be successfully re-induced multiple times, if fit and suitable for intensive treatment.

It does appear that the maximum benefit is seen with the first treatment and duration of CR is shortened in subsequent relapses. This may be secondary to the (i) abridged chemotherapy protocols (single course), (ii) development of comorbidities and impact of previous chemotherapies and (most likely) (iii) the evolution of disease with resistant sub-clones. Younger fitter patients will of course be candidates for allograft but our cases were not considered eligible due to age and/or co-morbidities.

Disclosures

Authors have no conflicts of interest.

Author contribution

Dr. Srivasavi Dukka collected the information on the case series, did literature review and compiled the Letter

Prof. David T. Bowen was the originator of the idea, consultant in charge of the patients in the case series and helped in editing and refining the Letter.

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