Clinical Paper

A Comparison of Inpatient and Outpatient-Based Chemotherapy Regimens for the Treatment of Acute Myeloid Leukaemia In The Elderly

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Abstract

Introduction: Acute myeloid leukaemia (AML) is an aggressive haematological malignancy which is more common in the elderly and has a poor 5-year survival. There are no established beneficial interventions to treat AML in elderly patients. It is unclear whether outpatient delivery of palliative chemotherapies could reduce the burden of disease and hospitalisation for this group.

Aims: To compare overall survival, response to treatment and supportive care needs between inpatient and outpatient-based treatments for AML in elderly patients.

Materials & Methods: We undertook a retrospective cohort study in the Haematology Department at Belfast City Hospital comparing overall survival (OS), treatment responses and supportive care needs between inpatient and outpatient treatments for AML in elderly patients. Consecutive entrants to outpatient and inpatient based clinical trials between February 2013 and January 2017 were included. Case notes, chemotherapy charts, clinic letters, blood bank and electronic care records were analysed.

Results: OS and rates of CR (complete remission), CRi (CR with incomplete count recovery) and PR (partial response) was not significantly different between inpatient and outpatient regimens with a median OS of 201 vs. 124 days, respectively. No response was observed in 35% of patients in the inpatient group compared with 65% of the outpatient group, however this did not reach significance. Of patients who achieved CR/CRi in the outpatient group, 75% relapsed at a median of 271 days, compared with 60% of the inpatient group at a median of 209 days. At least one grade 3-4 toxicity was experienced by 90% and 83.3% of inpatient and outpatient groups, respectively. There was no difference in six common grade 3-4 toxicities. Patients on the outpatient regimen spent fewer days in hospital but had a median packed red cell use of more than twice that of the inpatient group. No difference was noted in infections, days on antibiotics or platelet use.

Discussion: Our data suggests that outpatient chemotherapy is safe and can reduce hospitalisation for elderly patients with AML, without a decline in OS or response rates. These results provide an important rationale to test the comparative efficacy of outpatient chemotherapy. Chemotherapy related toxicities remain a significant source of morbidity in this population and highlight the need to develop novel, targeted therapies for this age group.

INTRODUCTION

Acute Myeloid Leukaemia (AML) is an aggressive group of haematological malignancies that are more common in the older population with a median age of onset at ~65years [1]. Despite recent therapeutic advances in younger patients, little improvement has occurred in the survival of older patients. Five year survival rates remain poor at ~5% in patients >60 years compared with up to 50% in younger patients [2,3]. It has been established that treatment of elderly patients with intensive chemotherapy is often futile, resulting in more early deaths and unacceptable toxicities compared with younger age group [4]. In addition, responses to chemotherapy are poorer and relapse rates are higher in older patients [5].

There are currently no established beneficial therapeutic interventions to treat AML in elderly patients and as such, enrolment in clinical trials investigating combinations of low dose chemotherapy is the recommended approach [3,6]. While determining the optimal chemotherapy regimens in the elderly has received much research interest, little attention

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has been paid to the clinical setting needed to support their delivery. It is unclear whether an outpatient delivery of such palliative regimens represents a treatment option which would potentially reduce the burden of hospitalisation and improve quality of life. To determine if chemotherapy regimens differ in efficacy or tolerability according to the clinical setting they are delivered in, we undertook a retrospective analysis of an outpatient based chemotherapy regimen (Phase II Randomised Trial of 5-Azacitidine versus 5-Azacitidine in combination with Vorinostat in patients with Acute Myeloid Leukaemia or High Risk Myelodysplastic Syndromes Ineligible for Intensive Chemotherapy- RAvVA trial) [7] and an inpatient based low dose chemotherapy regimen in patients with high risk MDS and AML unsuitable for intensive chemotherapy.

AIM & STUDY DESIGN

This was a retrospective cohort study carried out in the Haematology Department of Belfast City Hospital to compare overall survival, response to treatment and supportive care needs between inpatient and outpatient-based protocols for AML in elderly patients. Inpatient based treatment consisted of 4 cycles of low dose cytarabine (20mg BD subcutaneously, days 1-10) +/- another experimental drug at 28-42-day intervals as part of the AML- LI1 trial. Within the RAvVA outpatient trial, patients received either Azacitidine alone (75mg/m^2 days 1-9) or a combination of Azacitidine (75mg/m^2 days 1-9) + Vorinostat (300mg BD days 3-9 PO) for six 28-day cycles before assessment of response.

MATERIALS & METHODS

Patient selection

Inclusion criteria: Inpatient regimen included patients with newly diagnosed *de novo* or secondary AML (excluding Acute Promyelocytic Leukaemia; aPML) or high risk MDS (>10% blasts). Outpatient regimen included patients with *de novo* or secondary AML, including relapsed AML and able to undertake treatment on an outpatient basis. Inclusion criteria common to both groups include age >60, unfit for intensive chemotherapy and undergoing less intensive treatment within a clinical trial. All patients provided written informed consent.

Exclusion criteria: aPML or blast transformation of CML, previous cytotoxic chemotherapy or allogenic haematopoietic stem cell transplant for AML, concurrent active malignancy under treatment, pregnant or lactating, adults of reproductive potential not willing to use appropriate and effective contraception during the trial and specified time afterwards, serum creatinine of ≥175umol/L, AST ≥2.5 x ULN (Upper limit of normal) and/or ALP ≥2.5 x ULN, total bilirubin ≥1.5 x ULN unless due to Gilbert's syndrome, any active infection including fungal, bacterial and viral infections (HIV, Hepatitis), history of MI, unstable angina, cerebrovascular accident or TIA within 6 months. Further specific cardiac exclusion criteria were added for selected drugs used alongside low dose cytarabine in the inpatient regimen (Appendix 1).

APPENDIX 1:

Specific cardiac exclusion criteria for Ganetespib:

- Myocardial infarction within 12 months, uncontrolled angina within 6 months, current or history of congestive heart failure- New York Heart Association (NYHA) class 3 or 4 unless an echocardiogram or multiple gated acquisition scan performed either within 1 month prior to study screening or during screening results in a left ventricular ejection fraction that is >45% or institutional lower limit of normal value.

- Diagnosed or suspected long QT syndrome. Any history of clinically significant ventricular arrhythmia.

- Prolonged QTc interval on pre-entry ECG

- Uncontrolled hypertension

- Obligate need for a pacemaker

- Complete left bundle branch block

- Uncontrolled atrial fibrillation

Consecutive entrants to both trials between February 2013 and January 2017 were included. Baseline characteristics were compared across both groups. Co-morbidities were graded using the Haematopoietic Cell Transplant Comorbidity Index (HCT-CI) indicating severity of co-morbidity and risk of mortality (0= low risk, 1-2= intermediate risk, >2=high risk) [8]. Cytogenetic reports from Northern Ireland Regional Genetics Laboratory at Belfast City hospital were analysed using StarLims database and categorised into favourable, intermediate or poor cytogenetic risk.

Endpoints

Primary endpoint was overall survival (OS), measured from date of randomisation to trial as documented by Clinical Trials Nurse within patient notes, to date of death as documented on electronic care record (ECR). Alive patients were censored at date of analysis.

Response

Response to therapy was evaluated following each cycle of treatment on the inpatient regimen and after six cycles of the outpatient regimen. Response was categorised as Complete remission (CR), complete remission with incomplete recovery of neutrophils or platelets (CRi), partial remission (PR) or none. Patients who died during treatment before evaluation of response were classified as 'early deaths'[9]. Blood results of patients who experienced an 'early death' were analysed by a clinically trained researcher and further classified into 'Haematological Improvement' (HI) or 'no HI' depending on trends of blood counts during and following treatment. Duration of response was calculated from time of confirmed remission to date of relapse on bone marrow biopsies (blast count >5%).

Toxicity criteria

Data for reported toxicities was sourced from patient notes, clinic letters and discharge letters. Patients within the outpatient trial had chemotherapy charts in which toxicities

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were documented and graded by trained nursing staff. All toxicities were graded for severity using a scale from 1-4 as per National Cancer Institute Common Terminology Criteria for Adverse Events; NCI CTCAE v4 [10].

Supportive care needs

Blood product use including platelets and packed red cells (units), number of hospital admissions, number of days spent in hospital, infections and antibiotic use were documented using patient notes, blood bank records and ECR.

Statistical Analysis

Comparisons of baseline characteristics and supportive care requirements between RAvVA and the outpatient regimen were undertaken using the Mann-Whitney test. Kaplan-Meier curves were generated to depict overall survival in each group and overall survival was compared using the log rank test. Contingency analysis using the Chi-Squared test was undertaken to compare rates of response and the occurrence of severe toxicities in each group. For the purpose of these comparisons patients who died before undergoing a bone marrow biopsy were excluded from the analysis. All p-values reported are two-tailed, a p-value of < 0.05 was considered statistically significant.

TABLE 1:

Baseline Characteristics

	RAvVA	Inpatient Regime
N	17	20
Gender (%)	M= 71	M= 60
	F= 29	F= 40
	Median (SD)	
Age (years)	72 (7.3)	72 (4.0)
Blast (%)	33 (31.2)	49.5 (30.1)
WCC on presentation (x10⁹)	2.5 (14.0)	4.9 (14.3)
Platelets on presentation (x10⁹)	34 (57.6)	29 (36.5)
Haemoglobin on presentation (g/L)	93 (11.4)	95 (20.8)
	Severity of co-morbidity: HCT CI score* (no of patients)	
0 (low)	5	4
1-2 (intermediate)	5	7
>2 (high)	7	9

**HCT-CI (Haematopoietic Cell Transplant- Comorbidity Index) comprises 17 different categories of organ dysfunction and indicates severity of co-morbidities and risk of mortality.*

RAvVA trial= Randomised Trial of 5-Azacitidine versus 5-Azacitidine in combination with Vorinostat in patients with Acute Myeloid Leukaemia or High Risk Myelodysplastic Syndromes Ineligible for Intensive Chemotherapy

RESULTS

Description of study cohort

From an initial sample of 40 patients, a total of 37 patients were included, all of whom had a diagnosis of AML or high risk MDS between February 2013 and January 2017. Reasons for exclusion include one patient with age below 60 years, and two patients who were initially enrolled on the inpatient regimen and subsequently entered the outpatient RAvVA trial following relapse. For these patients, analysis was limited to outcomes whilst on inpatient regimen only. Seventeen patients were part of the RAvVA outpatient-based trial, and 20 patients had or were undergoing treatment as an inpatient receiving low dose chemotherapy at the time of the study. Baseline characteristics are summarised in Table 1. There were no significant differences between any of the variables analysed. Evaluation of cytogenetic risks in the inpatient regimen revealed 9 and 10 patients in the poor and intermediate categories, respectively, compared with 4 and 13 patients in the outpatient group (p=0.71). One patient had incomplete cytogenetic analysis due to poor quality metaphases on cell culture.

Overall survival

There was no significant difference in overall survival between inpatient and outpatient delivered regimens (Figure 1), with a median no. of days of 201 vs. 124, respectively; p=0.3284. Overall percentage survival at 1 year was 19% and 5% at 2 years, which is consistent with findings from similar studies [1,11,12].

Response

In those who underwent bone marrow examination rates of CR, CRi and PR (31%, 8% and 8% vs. 13%, 13% and 0%, respectively) were not significantly different between inpatient and outpatient groups overall. There was a nominally greater rate of patients with no response to therapy in the outpatient group (73%, n=11) than the inpatient group (54%, n=7) but this failed to reach statistical significance (p= 0.28). There was a trend to more early deaths in the inpatient group than the outpatient group (n= 7; 35% vs. n=2; 12%
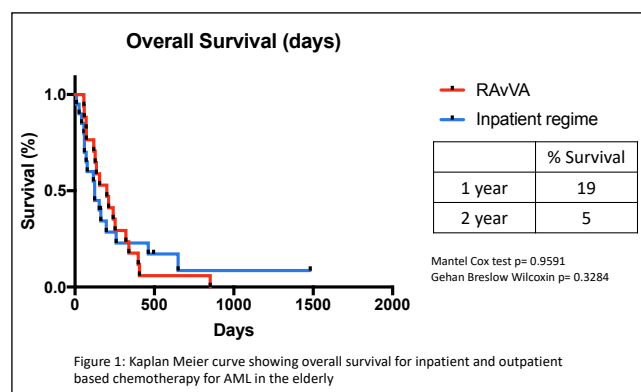

Figure 1: Kaplan Meier curve showing overall survival for inpatient and outpatient based chemotherapy for AML in the elderly

Fig 1. Kaplan Meier curve showing overall survival for inpatient and outpatient (RAvVA trial) based chemotherapy for AML in elderly

p=0.10). Further analysis of early deaths within both groups revealed a haematological improvement (HI) in one patient in both groups. It is possible that patients with early death and no HI may represent no response, therefore providing a potential explanation the lower rates of 'no response' in the inpatient group compared with the outpatient group. Of those who achieved CR or CRi in the outpatient group (n=4), seventy-five percent relapsed with an average time to relapse of 252 days (range 92-393). Sixty percent (n=3) of the patients who achieved CR or CRi in the Inpatient group relapsed with an average time to relapse of 236 days (range 170-330).

Toxicities

At baseline, 65.8% of all patients had a haemoglobin, white cell count or platelet count that would be classed as a grade 3 or 4 toxicity as per NCI common toxicity criteria. Further analysis was limited to non-haematologic toxicities, of which the majority were mild- moderate at grade 1-2 (73% and 59% of all reported toxicities in outpatient and inpatient regimen, respectively). Interestingly, 83.3% of patients in the outpatient and 90% of the inpatient group experienced at least one grade 3 or 4 toxicity which is defined as severe or life threatening. There were seven common grade 3 or 4 toxicities across both groups including sepsis, epistaxis, hypokalaemia, pulmonary oedema and fatigue (Table 2). There was no statistically significant difference between the two groups for any single grade 3/4 toxicity. Of note, over 50% of patients in both groups experienced life threatening sepsis.

Supportive Care Requirements

Unsurprisingly, patients treated on the outpatient regimen spent significantly less time in hospital with a calculated median number of days in hospital of 42 days compared with 80 days for inpatient group, including treatment days (p=0.0016). Both groups had a median of 2 hospitalisations, reflecting longer duration of in-hospital stay per admission on the inpatient regime. Despite this, packed red cell use was significantly higher in the outpatient group with a median of 26.5 units, compared with 12.5 units for the inpatient group (p=0.038). There was no difference between the outpatient and inpatient regimens for number of infections (median 3 vs. 2; p=0.96), days on antibiotics; (41.5 vs 41; p=0.54); or units of platelets required (15 vs 14, p=0.93), respectively.

TABLE 2:

Grade 3/4 Toxicities

Grade 3/4 Toxicity	IP regime	RAvVA
Sepsis	13	9
Epistaxis	3	2
Hypokalaemia	2	3
Pulmonary oedema	2	1
Hyponatraemia	2	1
Fatigue	1	1
Hypotension	1	1

DISCUSSION

We aimed to identify and characterise differences in outpatient and inpatient based chemotherapy regimens for elderly patients with AML. To our knowledge, this is the first study to compare clinical setting for delivery of palliative chemotherapy in this group. The average cost of treating elderly patients with AML has been estimated at around $42,000 in a US study [12]. Whilst treatment of AML has historically been associated with prolonged periods of hospitalisation, there has been much interest in shifting from inpatient to outpatient treatment to reduce medical resource utilisation and burden of hospitalisation [13]. Interestingly, a number of studies have been carried out which support early discharge of patients following intensive induction/ salvage chemotherapy for AML and suggest delivery of supportive care as an outpatient to be safe without negatively impacting on survival [14-16]. Similarly, the data presented here demonstrates no significant difference in the primary endpoint of overall survival or response to treatment between inpatient and outpatient delivery of chemotherapy (p= 0.3284). In keeping with the aim of reducing hospitalisation costs, there was a significant difference in the number of days spent in hospital with patients treated on the outpatient regimen spending on average less than half the time in hospital as patients on the inpatient regimen. Despite the observational nature of this study and baseline differences in patient characteristics, our work provides a rationale to explore the efficacy of this approach in interventional studies.

As with all types of chemotherapy, monitoring toxicity and prompt access to medical care is imperative. Analysis of toxicity and supportive care needs in this study revealed a high percentage of patients in both groups experiencing at least one life threatening or severe toxicity, with over half of the patients in both groups experiencing sepsis. Comparison between groups showed significantly more mild to moderate toxicities and higher packed red cell use in the outpatient group. Possible explanations for this include more reporting of toxicities as a result of close monitoring by day unit staff on a chemotherapy chart in the outpatient regimen, and also the preparation of 'standing orders' of packed red cells for patients receiving outpatient chemotherapy in a day unit. Furthermore, inclusion of 6 patients with relapsed AML in the RAvVA trial, and no participants with relapsed AML in the inpatient regimen may have constituted a subgroup of patients with more advanced disease and a higher requirement for blood product support. Nevertheless, this suggests that with delivery of an outpatient-based chemotherapy regimen, patient education on early recognition of chemotherapy related complications and sepsis is essential, as well as adequate facilities to provide supportive medical treatment as required.

This study has several limitations, including a small sample size and absence of a sample size calculation, reducing the external validity. We relied on accurate documentation of toxicities, blood product use and antibiotic duration on

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discharge letters, patient notes and chemotherapy charts, many of which were not intended for research purposes. Different combinations of chemotherapy were a baseline confounding variable.

CONCLUSION

Survival of elderly patients with AML remains unfavourable even with advances in treatments over recent decades. Despite less intensive treatments with palliative chemotherapy, the burden of toxicities and hospitalisations for patients in this age group is still noteworthy. We postulate that there may be a role for outpatient-based chemotherapy in reducing hospitalisations and enhancing quality of life for elderly patients with AML without a decline in overall survival or response rates. A larger scale randomised controlled trial to compare inpatient and outpatient delivery of chemotherapy would be a suitable way to clarify this further.

CONFLICTS OF INTEREST

M.F McMullin has been on a speakers bureau and received funding for travel to Celgene Conference.

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