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Outpatient Bendamustine and Idarubicin for Upfront Therapy of Elderly acute myeloid leukaemia/myelodysplastic syndrome: A Phase I/II Study using an Innovative Statistical Design

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Abstract

Combinations of agents may improve outcomes among elderly acute myeloid leukaemia (AML) and high-risk myelodysplastic syndrome (MDS) patients. We performed an adaptive phase I/II trial for newly-diagnosed AML or high-risk MDS patients aged ≥ 50 years using a Bayesian approach to determine whether 1 of 3 doses of bendamustine (45, 60, 75 mg/m² days 1–3), together with idarubicin (12 mg/m² days 1–2), might provide a complete response (CR) rate 40% with <30% grade 3–4 non-haematological toxicity. We treated 39 patients (34 AML; 5 MDS with >10% marrow blasts; median age 73 years). None of the 3 bendamustine doses in combination with idarubicin met the required CR and toxicity rates; the 75 mg/m² dose because of excess toxicity (2 of 3 patients) and the 60 mg/m² dose because of low efficacy (CR rate 10/33), although no grade 3–4 non-haematological toxicity was seen at this dose. Median survival was 7.2 months. All patients began treatment as outpatients but hospitalization was required in 90% (35/39). Although we did not find a dose of bendamustine combined with idarubicin that would provide a CR rate of >40% with acceptable toxicity, bendamustine may have activity in AML/MDS patients, suggesting its addition to other regimens may be warranted.

Keywords

AML; bendamustine; MDS; elderly; bayesian

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INTRODUCTION

For decades the cornerstone of acute myeloid leukaemia (AML) induction therapy has remained a combination of three days of an anthracycline and seven or ten days of cytarabine (*i.e.*, “3 + 7” or “3 + 10”) that can produce complete remissions (CR) in up to 85% of patients aged between 18 and 60 years.(Tallman *et al*, 2005; Lowenberg *et al*, 2003; Stone *et al*, 2004) However, inferior outcomes (lower CR rate, shorter remissions and survival) have been observed in the elderly.(Appelbaum *et al*, 2006a) Although to some extent this reflects a propensity to treatment-related mortality (TRM) in older patients, a more substantial problem is resistance to standard therapy, manifested as failure to enter CR despite not incurring TRM or as relapse. Resistance is well known to be associated with the complex cytogenetic abnormalities frequently seen in older patients and their frequent histories of antecedent haematological disorders or chemotherapy for other malignancies.(Appelbaum *et al*, 2006b; Appelbaum *et al*, 2006a) The poor response to standard treatment (*e.g.*, 3 + 7, 3 + 10, azacitidine, decitabine) in older patients has prompted recommendations that older patients participate in clinical trials whenever possible.(O'Donnell *et al*, 2012) Although molecularly targeted therapy appears an attractive option, this has largely been disappointing because targeting one abnormality, as has often been done, ignores the contribution of other abnormalities that may be present. Therefore, investigations of empiric applications of new therapeutics with unique mechanisms of action remain worthwhile.

Here we report use of bendamustine plus idarubicin in older patients with newly-diagnosed AML and high-risk myelodysplastic syndrome (MDS). Bendamustine may function both as an alkylating agent and a nucleoside analogue and has been effective in chronic lymphocytic leukaemia and non-Hodgkin lymphoma.(Cheson & Rummel, 2009; Rummel, 2008a; Rummel, 2008b) The drug may be associated with prolonged myelosuppression, a characteristic suggesting utility in AML.(Strupp *et al*, 2007) A 15-patient trial using bendamustine in relapsed/refractory AML did not produce CR, but did result in a decline in marrow blasts.(Strupp *et al*, 2007) Furthermore, bendamustine was well-tolerated, suggesting that higher doses might be used in combination with a standard agent, such as idarubicin, and that the bendamustine-idarubicin regimen might be given in the outpatient setting, an appealing possibility to many patients.

Novel drugs and drug combinations have conventionally been first tested in Phase I studies (dose finding decisions based solely on toxicity) with Phase II (efficacy) evaluations following as a separate trial; a stepwise process that may slow new drug advances.(Walter *et al*, 2010) Innovative designs that monitor both response and toxicity may thus increase efficiency. Specifically, these designs call for moving to larger trials only if efficacy is above a pre-specified minimum and toxicity is below a pre-specified maximum,(Estey & Thall, 2003) under the assumption that truly effective drugs will show activity even at doses below the maximum tolerated dose (MTD). We used such a design in this trial in which patients aged >50 years with newly-diagnosed AML or high-risk MDS (10–19% marrow blasts) received bendamustine plus idarubicin as outpatients. In this single-arm adaptive Phase I/II dose-escalation trial, we used a Bayesian approach to estimate the MTD of bendamustine associated with a CR rate of at least 40% and with <30% grade 3–4 non-haematological toxicity.(Wathen *et al*, 2008) The induction drugs were given in the

outpatient setting whenever possible, consistent with the current trend of chemotherapy administration.

MATERIALS AND METHODS

Patients and Treatment

Patients aged 50 years or greater with newly-diagnosed AML and intermediate- or poor-risk cytogenetics (CG) or high-risk MDS (10–19% bone marrow blasts) were eligible provided they had not received more than 1 course of hypomethylating agent for MDS. All patients received idarubicin at 12 mg/m² on days 1 and 2 and one of three doses of bendamustine (45, 60 or 75 mg/m² daily on days 1 to 5). Patients were entered in cohorts of 3 with the first cohort receiving 45 mg/m²; the dose in subsequent patients was dependent on the outcome in prior patients. The initial bendamustine dose was chosen based on data that suggested 400 mg/m² was an acceptable single-agent dose in AML (personal communication: M.H Kantarjian, MD Anderson Cancer Center, Houston, TX USA, 2010). The first cohort received approximately one-half (225 mg/m² per cycle) of this bendamustine dose combined with two-thirds (24 mg/m² per cycle) of the standard idarubicin dose. A bendamustine step-down dose of 30 mg/m²/day was allowed but never used. The study was approved by the Fred Hutchinson Cancer Research Center (FHCRC) Institutional Review Board and all patients provided written informed consent. National Cancer Institute (NCI) Clinical Trials Network identifier: NCT01141725.

Primary Objectives

The primary efficacy outcome was CR and the primary toxicity criterion was the presence of a grade 3 or 4 non-haematological dose-limiting toxicity (DLT) as outlined in the NCI Common Toxicity Criteria version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Patients were removed from study if they incurred DLT or were not in CR after 3 cycles. Responses were assessed using standard criteria.(Cheson *et al*, 2003)

Study Design and Statistical Considerations

The Bayesian trial design specified anticipated probabilities (*i.e.*, priors) of CR and DLT at the various bendamustine doses. While based on historical data, the priors were taken to be relatively non-informative because the regimen was new. As response and toxicity data became available for each cohort of 3 patients, Bayes theorem was used to update the priors (Table I) and derive current probabilities (*i.e.*, posteriors) of CR and/or DLT at each dose. These posteriors were primarily influenced by the actual data due to the non-informative priors. The posteriors were evaluated in relation to a minimum acceptable probability of CR of 40% and a maximum acceptable probability of toxicity of 30%, which was between the 1/6 considered acceptable and the 2/6 commonly considered unacceptable with the standard “3 + 3” Phase I design. The trial was to be stopped if the posteriors indicated a very low likelihood (<2% chance) that any dose was associated with both of these probabilities. Unless early stopping occurred (*i.e.*, <2% probability of both CR rate at least 40% and grade 3–4 toxicity <30%) this process was repeated iteratively to a maximum sample size of 48 patients. The CR and DLT parameters were chosen to give desirable probabilities of

selecting for future study doses meeting the minimum acceptable response and maximum acceptable toxicity rates.

RESULTS

Patient Characteristics

Between October, 2010 and May, 2012 39 patients with a median age of 73 years (range, 56–82) received therapy. The characteristics of these patients are described in Table II. AML comprised the majority of the cases (34 of 39 patients; 87%); among these 35% (12/34) had *de novo* AML, 47% (16/34) had an antecedent haematological disorder, and 18% (6/34) had received previous chemotherapy and/or radiation therapy for a prior malignancy. Five patients had high-risk MDS with more than 10% bone marrow blasts. Fifteen patients (38%) had unfavourable-risk CG defined as either complex (>3 anomalies; n=6) or monosomal karyotype (MK; n=9) and the remaining 24 (62%) had intermediate-risk CG as defined by Southwest Oncology Group criteria, (Slovak *et al*, 2000) including 8 (21%) with a normal karyotype. None of the latter had favourable molecular markers at the time of therapy (*NPM1* mutated/*FLT3* wild-type or double mutated *CEBPA*). Almost 50% of patients had one poor-risk factor independent of age over 60 years and 38% had two or more age-independent risk factors. Only 5 patients (13%) had age over 60 years (range, 62–79) as the sole poor-risk feature for this study. The median TRM score at the time of therapy among all patients was 5.2 (range, 0.5–20.5) predicting a less than 7% chance of death within 28 days of starting therapy with standard curative-intent induction chemotherapy. (Walter *et al*, 2011)

Number of Courses and MTD Estimation

Twenty-five patients (64%) received one course of treatment, 7 (18%) received two and 7 (18%) received three courses. The number of patients in each dosing cohort and treatment efficacy and toxicity are reported in Tables III and IV. The MTD of bendamustine in combination with idarubicin was estimated to be 60 mg/m²/day for 5 days; two cases of grade 3 toxicity occurred in the 3 patients entered at the 75 mg/m² dose with the DLT being congestive heart failure and mucositis in one patient each, leading to treatment of subsequent patients at the 60 mg/m² bendamustine dose. The cumulative incidence of grade 3/4 non-haematological toxicity was 5% (2 of 39 patients). Four patients (10%) in the 60 mg/m² cohort died within 28 days of starting therapy; 3 of these 4 patients had fatal infections and one died of complications related to an occluded femoral artery. The median TRM score of these 4 patients who died before day 28 was 2.62 (range, 1.66–3.16).

Tolerability, Outpatient Administration, and Hospitalization

All therapy was administered in the outpatient clinic but hospitalization was required in 90% of patients (35/39). The grade 3/4 adverse events and number of hospital admissions for each event seen among the 35 admitted patients are shown in Table V. The leading causes of admission were febrile neutropenia (26/35; 74%) and fungal infections (4/35; 11%). Patients spent an average of 7 days (range, 0–21) as an inpatient per cycle and the median number of days inpatient was 7. Sixty cycles of therapy were administered in total. In 51 cycles the

drug was started in the outpatient clinic, but only 22 cycles were completed entirely on an outpatient basis (Table VI).

Efficacy

The combination of bendamustine and idarubicin led to a CR in 11 (28%) patients and a CRi (CR with incomplete count recovery) in 2 (5%) additional patients for a composite CR/CRi rate of 33% (Tables III and IV). These analyses included all trial subjects, including the 2 patients whose outcome was unknown and were considered non-responders. Among 33 patients that received the MTD (60 mg/m² of bendamustine) the CR rate was 30% (10/33) with a combined CR/CRi rate of 36%. Three of the CR patients subsequently proceeded to allogeneic stem cell transplantation.

Influence of Cytogenetics on Outcome

Twelve of 24 patients (50%) with intermediate-risk CG achieved a CR, including 7 of 8 patients with normal CG; one patient with normal CG died of an acute myocardial infarction before disease assessment could be performed. Of the patients treated at the 60 mg/m² MTD level, 3 of 15 (20%) with unfavourable CG (including one case of MK) obtained a CR and 11 of 22 (50%) with intermediate CG were in CR after therapy ($p=0.05$, Fisher's exact test). Among all patients, the CR rate and overall survival (Fig. 1) were similar between patients with intermediate CG compared to those with an unfavourable karyotype.

DISCUSSION

Empiric drug combinations have been a historical instrument of advancement for leukaemia therapy. While there have been other trials using bendamustine to treat AML and MDS (Strupp *et al*, 2007), this study appears to be the first in which bendamustine was utilized as a frontline therapy in any myeloid stem-cell disease. Our data indicate that the principal feature that makes the bendamustine plus idarubicin combination attractive is that it can be administered in the outpatient department to patients with advanced age and has little toxicity at a bendamustine dose of 60 mg/m² daily $\times$ 5 days, at which it was associated with a CR rate of 30% (95% confidence interval [CI], 16–49%) and CR plus CRi rate of 36% (95% CI, 20–55%; Table IV). Although we did not have the data for a comparison *via* multivariate analysis with other outpatient regimens, such as decitabine or azacitidine, the response rate, survival and toxicity patterns with bendamustine plus idarubicin seem comparable to those seen with these treatments. It remains possible that a higher proportion of patients given bendamustine and idarubicin required hospitalization, but this is impossible to ascertain stressing the desirability of reporting time subsequently spent in hospital after administration of outpatient regimens, although admittedly this time might vary according to institutional practice. It is also difficult to know whether bendamustine added much to the use of idarubicin alone, or *vice versa*. More importantly, however, the CR, and particularly survival rates, with each of the various outpatient regimens seems unsatisfactory. Indeed our study closed before accrual of the maximum sample size because the likelihood of a 40% CR rate at any of our 3 bendamustine doses was very low. Possible means of improving outcome with the regimen might be to extend the duration of idarubicin to 3 days or that of bendamustine at 60 mg/m² to 7 days. It might also be useful to add bendamustine to other

AML regimens. Enthusiasm for these approaches, however, might be tempered given that the response rate with bendamustine and idarubicin was higher in patients with normal rather than unfavourable CG, suggesting that the regimen may not be qualitatively different than more standard regimens from which the prognostic significance of CG was derived.

We found the design we used attractive in at least two regards. First, as the data were used to adjust posterior probabilities at each of the 3 doses, it allowed for dose cohorts that were “closed” previously to be re-visited. For example, if toxicity at the lower doses appeared minimal as patients continued to be accrued at these doses, this scenario would be desirable because it is well-known that toxicity depends not only on the drug dose, but also on the characteristics of patients treated at that dose. Thus, the observation of toxicity in 2 of 3 patients at a dose might reflect the age of the patients, but not the actual dose. A second appealing feature was that the design obviated the need to perform separate Phase 1 and Phase 2 trials. It did so by assuming that responses could occur at doses below the MTD. Of course, this assumption would not be made in a standard Phase 1 design and thus, response would only be monitored once a Phase 2 trial began. However, it seems plausible that with truly effective drugs responses may be seen below the MTD. The extent to which this occurs seems worthy of systematic investigation.

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Kaplan-Meier Plot of Overall Survival

Figure 1.

Overall survival of acute myeloid leukaemia patients, comparing those with intermediate-risk cytogenetics to those with unfavourable cytogenetics, including those with monosomal karyotype. Transplanted patients (n=3) were censored in the Kaplan-Meier graph.

Table I

Prior Probabilities of Toxicity and Response.

Bendamustine Dose Cohort	Prior Probability of Toxicity	Prior Probability of Response
<i>Cohort A 45 mg/m² (n=3)</i>	0.10	0.15
<i>Cohort B (D) 60 mg/m² (n=33)</i>	0.20	0.25
<i>Cohort C 75 mg/m² (n=3)</i>	0.25	0.45
<i>Cohort E 90 mg/m² (n=0)</i>	0.40	0.60

Table II

Patient Characteristics

Bendamustine Dose Cohort (number of patients treated)	Cohort A 45 mg/m ² (n=3)	Cohorts B and D 60 mg/m ² (n=33)	Cohort C 75 mg/m ² (n=3)	All Patients (n=39)
Median Age (range); years	69 (67–74)	73 (56–82)	78 (69–79)	73 (56–82)
Gender (male; n)	2	22	0	24
Median WBC (range) at diagnosis ×10 ⁹ /l	2.0 (1.5–2.5)	3.0 (1.0–17.3)	1.3 (0.3–21.7)	2.9 (0.4–21.8)
AML, n (%)	3 (100)	28 (85)	3 (100)	34 (87)
Secondary AML - Prior therapy	0 (0)	5 (15)	1 (33)	6 (15)
Antecedent Haematological Disorder	2 (67)	13 (33)	1 (33)	16 (41)
Cytogenetic Risk Group, n (%)				
Intermediate	0 (0)	22 (67)	2 (67)	24 (62)
Unfavourable	3 (100)	11 (33)	1 (33)	15 (38)
Peripheral Blasts, n (%)	2 (1–27)	13 (0–76)	17 (0–40)	11 (0–76)
High-Risk MDS (10–19% marrow blasts)				
RAEB-2 (WHO classification)	0 (0)	5 (15)	0 (0)	5 (13)
Revised IPSS	N/A	6.5 (6–8)	N/A	6.5 (6–8)
High	N/A	2	N/A	2 (5)
Very high	N/A	3	N/A	3 (8)
ECOG Performance Status, n (%)				
0	0 (0)	0 (0)	0 (0)	0 (0)
1	2 (67)	30 (91)	3 (100)	35 (90)
2	1 (33)	3 (9)	0 (0)	4 (10)
Poor Risk Features *				
Age only	0 (0)	4 (12)	1 (33)	5 (13)
1 (age-independent)	0 (0)	18 (55)	1 (33)	19 (49)
2 (age-independent)	3 (100)	11 (33)	1 (33)	15 (38)
Median TRM score (range)	3.13 (0.97–4.16)	2.83 (1.55–10.6)	2.16 (1.74–2.96)	2.83 (0.97–10.6)
Median number of cycles delivered (range)	1	1 (1–3)	1 (1–3)	1 (1–3)

* Poor-risk features including: 1) age ≥ 60 years; 2) secondary AML (MDS/AML, myeloproliferative disease/AML, treatment-related AML); and/or 3) adverse cytogenetics. AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; WBC, white blood cell count; RAEB-2, refractory anaemia with excess blasts, type 2; WHO, World Health Organization; IPSS, International Prognostic Scoring system; ECOG, Eastern Cooperative Oncology group; TRM, treatment-related mortality; N/A, not applicable.

Table III

Cohort Progression

Cohort	Patient Number	Bendamustine Dose (mg/m ²)	Age (years)	TRM Score*	Evidence of Efficacy	Evidence of Toxicity
A	1	45	67	4.16	No	No
	2		69	0.97	No	No
	3		74	3.13	No	No
B	4	60	68	3.39	Yes (CR)	No
	5		63	3.15	No (CR)	No
	6		78	2.16	No	No
C	7	75	77	4.70	No	Yes
	8		79	2.96	Yes (CR)	No
	9		69	1.74	No	Yes
D	10	60	67	4.49	Yes (CR)	No
	11		71	2.56	No	No
	12		77	2.66	Yes (CR)	No
	13		68	3.20	Yes (CR)	No
	14		79	2.86	No	No
	15		71	2.78	No	No
	16		76	2.01	No	No
	17		74	5.25	No	No
	18		81	2.70	Yes (CR)	No
	19		62	2.80	No	No
	20		68	2.80	No	No
	21		62	3.12	No	No
	22		67	2.98	Yes (CR)	No
	23		76	3.01	Yes (CR)	No
	24		68	2.80	Yes (CR)	No
	25		78	2.09	Unknown	No
	26		72	2.12	No	No

Cohort	Patient Number	Bendamustine Dose (mg/m ²)	Age (years)	TRM Score *	Evidence of Efficacy	Evidence of Toxicity
	27		62	2.38	No	No
	28		75	3.22	Yes (CR)	No
	29		74	3.40	Unknown	No
	30		56	1.75	No (CRi)	No
	31		71	2.83	No	No
	32		78	1.94	No	No
	33		73	1.50	No	No
	34		61	3.36	Yes (CR)	No
	35		78	1.94	Unknown	No
	36		73	3.16	Unknown	No
	37		74	10.6	Unknown	No
	38		74	1.66	Unknown	No
	39		82	3.39	No	No

* treatment-related mortality score for each patient with associated % chance of death within 28 days of starting therapy.(Walter *et al*, 2011). CR, complete response.

Table IV
Response Characterization and Clinical Toxicity Outcomes Following Bendamustine and Idarubicin Administration

<i>Bendamustine Cohort</i>	<i>Cohort A 45 mg/m² (n=3)</i>	<i>Cohorts B and D 60 mg/m² (n=33)</i>	<i>Cohort C 75 mg/m² (n=3)</i>	<i>All patients (n=39)</i>	<i>Median age, years (range)</i>
<i>Toxicity</i>	0 (0%)	0 (0%)	2 (66%)	2 (5%)	
<i>Efficacy</i>					
CR	0 (0)	10 (30)	1 (33)	11 (28)	72 (56–81)
CRi	0 (0)	2 (6)	0 (0)	2 (5)	66 (56–76)
CR + CRi	0 (0)	12 (36)	1 (33)	13 (33)	68 (56–81)
No CR	3 (100)	21 (64) [*]	2 (67)	24 (67)	73 (62–82)

CR, complete response; CRi, CR with incomplete count recovery.
* Includes 6 patients with unknown response (e.g., due to early death).

Table V

Grade 3/4 Adverse Events and Hospital Admissions Seen in 35 of 39 Patients

Admit Diagnosis	Number of Admissions (%)	Number of Patients (%)
Febrile Neutropenia	26 (54)	29 (74)
Fungal Infection	4 (8)	4 (11)
Pneumonia	2 (4)	2 (5)
Cellulitis	2 (4)	2 (5)
Bacteraemia	2 (4)	2 (5)
Sepsis	2 (4)	2 (5)
Sinusitis	1 (2)	1 (3)
Platelet Transfusion Refractory	1 (2)	1 (3)
Heart Failure	1 (2)	1 (3)
Atrial Fibrillation	1 (2)	1 (3)
Severe Mucositis	1 (2)	1 (3)
Intracranial Bleeding	1 (2)	1 (3)
<i>Clostridium difficile</i> Infection	1 (2)	1 (3)
Hypoxia	1 (2)	1 (3)
Dehydration	1 (2)	1 (3)
Acute Renal Injury	1 (2)	1 (3)

Table VI**Outpatient Cycles Administered and Time Spent Hospitalized**

Median days inpatient (range)	7 (0–21)
Average days inpatient (range)	7 (0–21)
Total number of cycles started as outpatient	51
Total number of cycles completely administered as outpatient	22
Average number of admission days per cycle	10 (1–22)