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Relationship between baseline white blood cell count and renal and hepatic function in older patients with acute myeloid leukemia☆☆

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ABSTRACT

Background: In a phase III trial, older patients with acute myeloid leukemia ($N=485$) received decitabine or treatment choice (supportive care or cytarabine). This post hoc analysis examined whether baseline renal and hepatic function and white blood cell (WBC) counts predicted response.
Methods: Baseline WBCs and renal and liver function markers were tabulated for responders/nonresponders.
Results: Nonresponders had higher mean baseline creatinine ($P=0.005$). Creatinine data showed no significant between-group differences by treatment within responder category.
Conclusions: No relationship was found between baseline WBCs or hepatic function and response. Higher baseline creatinine in nonresponders may not be clinically relevant.

1. Introduction

Acute myeloid leukemia (AML) is a common adult leukemia, with ≈12,330 new cases reported annually in the United States [1] and ≈18,000 new cases reported annually in the European Union [2]. While AML is more common in the elderly [3], treatments for these patients are limited, especially for patients with poor performance status and/or comorbidities. The US National Comprehensive Cancer Network [3] and the European LeukemiaNet [4] recently updated their AML treatment guidelines to include low-intensity cytarabine, 5-azacytidine, and decitabine as recommended therapies for these patients.

Decitabine, a hypomethylating agent, is indicated in the US for the treatment of de novo and secondary myelodysplastic syndrome of all French–American–British (FAB) subtypes and for intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups [5]. In Europe, decitabine is used to treat adults aged ≥65 years with newly diagnosed or secondary AML (according to World Health Organisation [WHO] classification) who are not eligible for initial treatment with standard chemotherapy [6].

A phase III trial was conducted in 485 patients aged ≥65 years with newly diagnosed AML [7]. Every 4 weeks, patients received decitabine 20 mg/m^2 (1-h intravenous infusion for 5 successive days) or patient's choice of treatment, with physician's advice, with either supportive care (SC) or cytarabine (20 mg/m^2 subcutaneous injection daily for 10 successive days) [7]. This post hoc analysis of this patient population examined whether baseline renal and hepatic function and white blood cell (WBC) counts are associated with response to decitabine or treatment choice.

2. Materials and methods

For patients with available data, baseline WBC count and markers of renal function (blood urea nitrogen [BUN], creatinine, and creatinine clearance) and of hepatic function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, and

Abbreviations: ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, complete response; CRi, complete response with incomplete blood count recovery; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FAB, French–American–British classification; PR, partial remission; SC, supportive care; WBC, white blood cell

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albumin) were compared for patients with and without a response to decitabine or treatment choice. Response was defined as morphologic complete remission (CR), CR with incomplete blood count recovery (CRi), or partial remission (PR), with morphologic CR defined per the International Working Group 2003 criteria [7,8]. Comparisons between responders and nonresponders were made and *P* values calculated using a 2-sided *t* test assuming unequal group variances (significance level <0.05). Creatinine levels were also analyzed at baseline and day 1 of each cycle, stratified by response and treatment group, using a 2-sided *t* test assuming unequal group variances.

Baseline creatinine levels were analyzed using logistic regression analysis based on responders (CR+CRi+PR) vs nonresponders, Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥ 2 vs 0–1, and FAB subtype M4/M4eos/M5 vs others (excluding patients with missing FAB subtypes).

3. Results

A total of 485 patients were randomized to either decitabine ($n=242$) or treatment choice ($n=243$) in the phase 3 trial [7]. At baseline, the median age of patients was 73 years (range, 64–89 years) in the decitabine group and 73 years (range, 64–91 years) in the treatment choice group. In the decitabine and treatment choice groups, respectively, median time since AML diagnosis was 14 days (range, 3–346) and 15 days (range, 0–398), and 36% and 35% of patients had secondary AML. In the decitabine group, 44% of patients had more than 50% bone marrow blasts and median white blood cell count was 3.10 (0.3–127.0) 10^9/L. In the treatment choice group, 42% of patients had more than 50% bone marrow blasts and median white blood cell count was 3.69 (0.5–80.9) 10^9/L. In each group, 36% of patients had poor-risk cytogenetics [7].

Overall, 102 of 485 patients (21.2%) were responders (CR+CRi+PR), including 68 of 242 patients (28.1%) in the decitabine group and 34 of 243 patients (14.0%) in the treatment choice group.

Baseline WBC count and baseline measures of hepatic and renal function for responders and nonresponders are shown in Table 1. No relationship was evident between responders to decitabine or treatment choice and baseline WBC counts, or between responders and baseline measures of hepatic function (ALT, AST, total bilirubin, and albumin). Regarding renal function (BUN, creatinine, creatinine clearance), nonresponders had a significantly higher mean baseline creatinine level compared with responders (86.78 vs 80.23 μmol/L, respectively; $P=0.005$), and correspondingly lower, although not significantly, creatinine clearance (68.35 vs 72.42 μmol/L, respectively; $P=0.067$). However, no significant difference between nonresponders and responders was noted in mean baseline BUN (6.97 vs 6.48 mmol/L, respectively; $P=0.067$) [7].

An analysis was also conducted on creatinine data for responders and nonresponders by treatment group (decitabine vs treatment choice). Mean baseline creatinine levels ($\pm$ standard deviation) by treatment group were 78.81 ± 15.78 μmol/L for decitabine responders ($n=68$) and 83.06 ± 23.94 μmol/L for treatment choice responders ($n=34$). Corresponding levels for nonresponders were 85.78 ± 26.99 μmol/L for decitabine ($n=171$) and 87.62 ± 27.19 μmol/L for treatment choice ($n=206$). No significant differences were seen when treatment groups were compared within responder categories.

Changes in creatinine levels over time by response to decitabine or treatment choice (Fig. 1) showed no clear trends or differences in change from baseline in creatinine levels between responders and nonresponders by treatment group.

Table 1
Relationship between response to decitabine or treatment choice and baseline white blood cell count, hepatic function (ALT, AST, bilirubin, and albumin), and renal function (BUN and creatinine) in older patients with acute myeloid leukemia.

Parameter	Nonresponder to Decitabine or Treatment Choice[a]	Responder to Decitabine or Treatment Choice[a] (CR+CRi+PR)	*P* value[b]
WBC (10^9/L)			
N	372	101	
Mean (SD)	9.25 (13.98)	7.02 (12.25)	0.117
Median (range)	4 (0.3–127)	3 (0.4–96)	
ALT (U/L)			
N	372	100	
Mean (SD)	25.32 (35.53)	20.79 (14.53)	0.054
Median (range)	18 (5–614)	17 (6–103)	
AST (U/L)			
N	371	101	
Mean (SD)	23.82 (15.93)	21.74 (9.84)	0.106
Median (range)	20 (5–203)	18 (9–65)	
Total bilirubin (μmol/L)			
N	376	100	
Mean (SD)	10.00 (5.06)	10.8 (5.20)	0.174
Median (range)	9 (3–33)	10 (3–29)	
Albumin (g/L)			
N	377	102	
Mean (SD)	34.18 (5.47)	35.07 (5.34)	0.140
Median (range)	35 (19–48)	36 (16–44)	
BUN (mmol/L)			
N	377	102	
Mean (SD)	6.97 (2.65)	6.48 (2.27)	0.067
Median (range)	6 (1–23)	6 (3–20)	
Creatinine (μmol/L)			
N	377	102	
Mean (SD)	86.78 (27.08)	80.23 (18.88)	0.005
Median (range)	81 (38–254)	78 (44–169)	
CrCL (mL/min)[c]			
N	377	102	
Mean (SD)	68.35 (19.32)	72.42 (19.83)	0.067
Median (range)	67 (23–138)	67 (33–133)	

ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, complete remission; CRi, CR with incomplete blood count recovery; CrCL, creatinine clearance; PR, partial remission; SD, standard deviation; WBC, white blood cell.

[a] Either supportive care or cytarabine.
[b] 2-sided *t* test assuming unequal group variances.
[c] Calculated using the Cockcroft–Gault method.

Logistic regression analysis showed that if baseline creatinine levels increased 1 unit, the odds of achieving a response were 0.988. Additionally, patients with "other" FAB classifications were less likely than patients with M4/M4E0/M5 to respond (odds ratio=0.807) to treatment, and patients with ECOG PS ≥ 2 were less likely to respond than patients with ECOG PS 0–1 (odds ratio=0.861). Compared with patients receiving SC, patients receiving decitabine were 3.144 times more likely to respond, and patients receiving cytarabine were 1.44 times more likely to respond.