Platelet recovery after the first cycle of DA chemotherapy for AML is an independent predictor of survival

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Background

The European Leukaemia Network divides treatment outcomes for AML post-chemotherapy into complete remission (CR), complete remission with incomplete count recovery (CRi), partial remission (PR) and refractory based on residual blast percentage, and platelet and neutrophil recovery. [1] CRi is similar to true CR in that morphological assessment of the post-chemotherapy bone marrow reveals a blast percentage of <5%, though a residual absence of platelet recovery to 100x10⁹/L and/or neutrophil recovery to 1x10⁹/L remains. Notably, previous literature has not specified a time point for which these thresholds must be achieved. While overt refractoriness to the first cycle of AML induction therapy is an established predictor of poor outcome, the remaining categories define a heterogeneous population with large variations in survival outcome. Remission status is classically used among these patients to predict overall survival, however explicit haematological count recovery following intensive chemotherapy may provide a more clear alternative to define prognostic groups, having already shown to be an independent predictor of overall survival following stem cell transplantation. [2]

Aims and Objectives

We aimed to clarify the value of a day-30 platelet count post-cycle 1 induction chemotherapy as a predictive indicator of overall survival (OS) in AML patients, and subsequently identify potential patient and disease factors that were associated with count recovery delay.

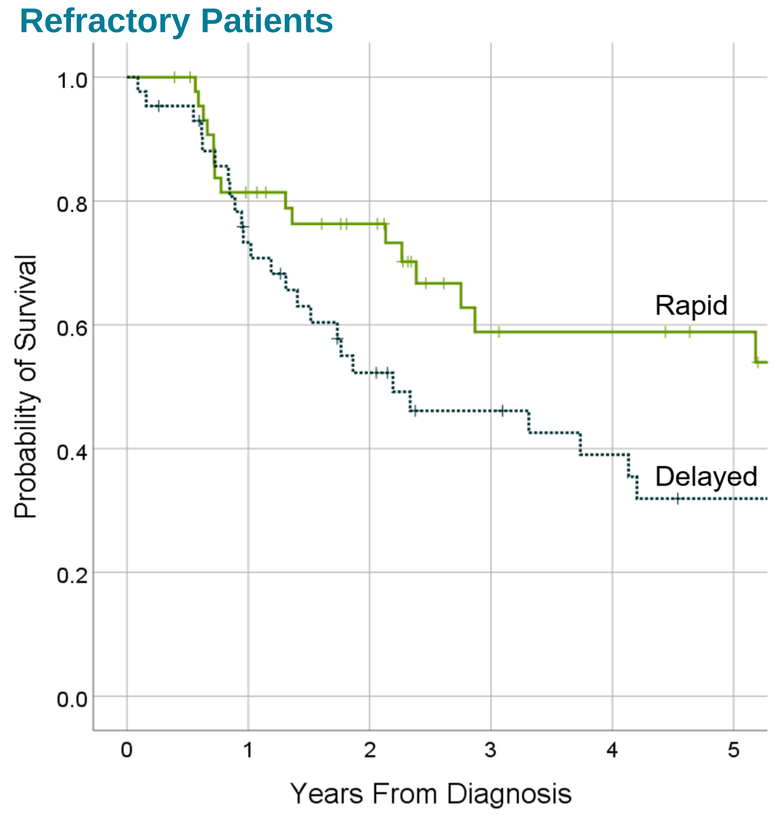
Methods

All non-M3 adult patients undergoing DA induction therapy for AML between January 2006 and December 2018 with full data available for review were entered into the study. Count recovery was retrospectively analysed and designated as ‘delayed’ or ‘rapid’ based on the isolated day-30 platelet count after the first induction cycle of chemotherapy, stratified relative to the median platelet count of the cohort. The primary outcome was overall survival at three years. Differences in the distribution of patient and disease characteristics between count recovery groups were then assessed. Factors included in multivariate analysis included blast count at diagnosis and cytogenetic risk category alongside count recovery as these factors were deemed to affect survival in the cohort significantly (p≤0.05). Factors previously established to independently affect survival in AML patients were also included in multivariate analysis; age at diagnosis, performance status, primary or secondary disease status, WHO category (due to survival associations of the sub-categories ‘AML with myelodysplasia-related changes’ and ‘therapy-related AML’) and post-chemotherapy MRD status. [3-7].

Results

112 patients were eligible for the study. Of these, 23 were refractory to the first induction chemotherapy cycle, and 89 achieved complete or partial remission. The 3-year OS was significantly worse in refractory patients, but no significant survival differences were seen between CR and PR groups (3-year OS: 55.6% (95% CI 42.3-68.9%), 48.3% (95% CI 26.0-70.6%) and 16.4% (95% CI 0.0-32.9%) for CR, PR and refractory groups respectively). Among all non-refractory patients, including those in partial remission, the median day-30 platelet count was 261 x 10⁹/L (n=89).

Fig 1: Overall Survival in Rapid versus Delayed Platelet Recovery Groups Amongst All Non-Refractory Patients



Delayed platelet count recovery was significantly associated with poorer OS in non-refractory patients (p=0.024) and maintained independent prognostic significance in multivariate analysis (HR 2.21, CI 1.17-4.17; p=0.015). 3-year OS was 58.8% (95% CI 41.9-75.7%) in the rapid count recovery group and 46.1% (95% CI 30.0-62.3%) in the delayed.

The frequency of AML patients with myelodysplasia-related changes and secondary disease was significantly higher in the delayed count recovery group, as was those with positive minimal residual disease status. Delayed recovery was further associated with older age at diagnosis and a higher day-30 post-chemotherapy CRP.

Characteristic	Plt > 261x10⁹/L (Rapid Recovery)	Plt < 261x10⁹/L (Delayed Recovery)	P Value
Age at diagnosis, years			
Median	55	59	0.016
Range	22 to 72	32 to 76	
WHO Category, n (%)			
AML with recurrent genetic abnormalities	20 (44.4)	8 (18.2)	
AML with myelodysplasia-related changes	6 (13.3)	18 (40.9)	
Therapy-related myeloid neoplasms	0 (0.0)	3 (6.8)	0.002
AML, not otherwise specified	18 (40.0)	14 (31.8)	
Unknown/Unavailable	1 (2.2)	1 (2.3)	
Primary or Secondary Disease, n (%)			
Primary	43 (95.6)	32 (72.7)	0.003
Secondary	2 (4.4)	12 (27.3)	
Day-30 CRP, mg/L			
Median	9.5	28.8	0.001
Range	0.2 to 134.0	1.0 to 255.7	
Post-Cycle 1 MRD Status, n (%)			
Negative	25 (55.6)	14 (31.8)	
Positive	18 (40.0)	29 (65.9)	0.017
Unknown/Unavailable	2 (4.4)	1 (2.3)	

Table 1: Distribution of characteristics among rapid and delayed groups

Conclusion

Considering all the potential variables with the ability to influence survival, it was striking that a singular platelet count at day 30 of cycle 1 induction therapy offered such significant prognostic information, even amongst patients achieving only partial remission. Platelet recovery to within the normal range may be a more suitable prognostic indicator than the existing 100x10⁹/L ELN threshold, however a spectrum of response was evident, with those in the highest and lowest quartiles of platelet count recovery exhibiting the most extreme differences in survival. Post-chemotherapy platelet count offers an accessible index with potential utility in the prognostication of non-refractory patients.

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