Original Study

Absolute Lymphocyte Count at Day 29 of Treatment Is a Powerful Predictor of Outcome in Multiple Myeloma

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Abstract

Multiple myeloma is a malignancy of the bone marrow. Despite advances, the overall prognosis remains poor with median survival of 4-5 years. In a retrospective analysis of 38 patients, we find that the day 29 lymphocyte count, measured four weeks after starting treatment, can powerfully predict prognosis. This simple test can guide optimal management and yields insights into the disease.

Background: Survival outcomes for patients who receive treatment for newly diagnosed multiple myeloma (MM) are highly variable. **Patients and Methods:** We conducted a retrospective analysis of 38 unselected MM patients who received treatment with cyclophosphamide, thalidomide, and dexamethasone to evaluate the prognostic value of the absolute lymphocyte count at diagnosis and at the end of the initial cycle of treatment defined as day 29, termed ALC-29. The median follow-up was 54 months (range, 2-83 months). **Results:** We found that ALC-29, as a continuous variable, was a predictor of overall survival (OS) in MM patients (hazard ratio, 0.208; 95% confidence interval, 0.093-0.689; $P = .007$). Patients with an ALC-29 $\geq 0.8 \times 10^9$/L (n = 16) experienced a superior median OS compared with patients with an ALC-29 $< 0.8 \times 10^9$/L (n = 22) with a median OS of 58.3 months versus 42.5 months respectively ($P = .006$). Multivariate analysis confirmed that ALC-29 $\geq 0.8 \times 10^9$/L was an independent prognostic indicator of OS in our cohort of MM patients. **Conclusion:** We concluded that the ALC-29 is a useful and simple predictor of outcome in newly diagnosed MM patients who receive standard chemotherapy. Our results support the hypothesis that host immunity plays an important role in tumor control in MM.

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Introduction

In the setting of autologous and allogeneic stem cell transplantation, absolute lymphocyte count (ALC) recovery has been identified as an independent prognostic indicator for clinical outcome in multiple hematological malignancies,[1-5] and in solid tumors.[6-9] These studies suggest that rapid immune reconstitution might increase a graft-versus-cancer effect, or decrease morbidity related to poor engraftment. More recently, evidence has highlighted ALC recovery as a powerful, independent prognostic factor for survival in the nontransplant setting, in patients who undergo intensive chemotherapy for treatment in acute myeloid leukemia (AML),[10-12] and B-cell lymphoma.[13,14] Results of several studies suggest that ALC at the time of diagnosis in multiple myeloma (MM) correlates with improved survival.[15,16] However, the prognostic value of the ALC at the end of the first 4-week cycle of treatment in MM has not been described in the literature. We sought to assess whether the ALC at day 29 (ALC-29) correlates with survival in patients with previously untreated MM who were treated at our hospital institution.

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Patients and Methods

Patient Population

Between 2005 and 2008, 45 consecutive patients with MM were evaluated at the Royal Sussex County Hospital (RSCH), Brighton, United Kingdom. To be included in the study, patients were required to be originally diagnosed, followed, and treated at the RSCH. Patients were excluded from the study if they refused chemotherapy (3 patients) or had a concomitant malignant diagnosis or complication of amyloidosis at the time of diagnosis (3 patients). Of the total of 39 eligible patients entered into the study, 1 patient had missing data and was excluded. Thus, our study

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sample comprised 38 MM patients (84%). All patients gave written, informed consent allowing the use of their medical records for medical research. The study was performed with institutional review board approval by the RSCH ethics committee and was conducted in accordance with the Declaration of Helsinki.

Chemotherapy

Nine patients received chemotherapy with CTD (cyclophosphamide, thalidomide, and dexamethasone). The CTD regimen consisted of a 21-day cycle of oral cyclophosphamide 500 mg once weekly; thalidomide 100 mg/d (increased to a maximum of 200 mg/d after first cycle if tolerated) continuously; and dexamethasone 40 mg/d on days 1 to 4 and 9 to 12 of each 21-day cycle. The remaining 29 patients received the CTD attenuated regimen (CTDa) based on age considerations, comorbidities, unsuitability for autograft consolidation, or patient preference for a less intensive regimen. The CTDa regimen consisted of a 28-day cycle of cyclophosphamide 500 mg once weekly; thalidomide 50 mg/d (increased to 100 mg/d after first cycle if tolerated); and dexamethasone 20 mg on days 1 to 4 and days 15 to 18.

End Points

The primary end point of the study was to assess the effect of ALC-29 for MM patients on overall survival (OS). The secondary end point was to determine whether the ALC-29 was an independent prognostic factor for OS in MM patients.

Prognostic Factors

The prognostic factors used in the study were age ($\geq$ 65 vs. $<$ 65 years), albumin ($<$ 35 g/L), and serum paraprotein level and type (immunoglobulin [Ig]G, IgA, κ/λ light chain). Age, sex, initial white cell count, treatment protocol, date of relapse, serum paraprotein, creatinine, albumin, calcium, alkaline phosphatase, urine paraprotein, survival status, ALC, absolute neutrophil count (ANC), and platelet count (Plts) on days 1 and 29 after intensive chemotherapy were also recorded.

Statistical Analysis

The OS was estimated using the methods of Kaplan and Meier,[17] and was measured from the date of MM diagnosis to the date of death or last follow-up. Differences between survival curves were assessed for statistical significance using the 2-tailed log-rank test. ALC was assessed as a continuous variable and dichotomized, based on finding the optimal cutoff point based on the log-rank statistics.[18] Univariate and multivariate analysis was performed using the Cox proportional hazards model, and hazard ratios (HRs) were estimated with 95% confidence intervals.[19] χ^2 tests were used to determine relations between categorical variables, and Spearman correlation coefficient was used for continuous variables. All P values represented were 2-sided, and statistical significance was declared at $P < .05$. Statistical analysis was undertaken using SPSS version 19.0 statistical software (SPSS Chicago, IL).

Results

Patient Characteristics at Diagnosis

The median age for the study group was 69 years (range, 37-2 years) at the time of diagnosis. The median follow-up was 54 months (range, 2-83 months). Distributions of additional baseline characteristics for these patients are presented in Table 1 and are summarized based on whether patients had an ALC-29 $\geq 0.8 \times 10^9$/L versus $< 0.8 \times 10^9$/L at day 29. Seven patients underwent autologous stem cell transplantation (ASCT). No patients were lost to follow-up. To address the possibility that the ALC-29 simply reflected bone marrow activity, we analyzed the ANC/Plts at the same time points as for ALC. No associations were identified between ANC or Plts and ALC at day 1 (ANC at day 1: $r_s = -0.266$; $P = .107$; Plts at day 1: $r_s = 0.149$; $P = .372$); and ALC-29 (ANC at day 29: $r_s = -0.136$; $P = .414$; Plts at day 29: $r_s = 0.050$; $P = .767$).

Table 1 Baseline Characteristics of Patients With ALC-29 $\geq 0.8 \times 10^9$/L and ALC-29 $< 0.8 \times 10^9$/L

Characteristics	ALC-29 $\geq 0.8 \times 10^9$/L (n = 16)	ALC-29 $< 0.8 \times 10^9$/L (n = 22)	*P*
Median Age (Range), Years	66 (37-80)	71 (57-82)	.080
Age, Years			.080
≥65	8 (50%)	5 (23%)	
<65	8 (50%)	17 (77%)	
Sex			.360
Male	7 (32%)	13 (59%)	
Female	9 (68%)	9 (41%)	
Median Albumin (Range), g/L	40.5 (25-47)	39.5 (27-46)	.546
≥35	13 (81%)	15 (68%)	
<35	3 (19%)	7 (32%)	
Median Alkaline Phosphatase (Range), i.u./L	75 (36-166)	91 (38-188)	.421
Median Calcium (Range), mmol/L	2.36 (1.81-2.43)	2.32 (1.83-2.97)	.624
Median Creatinine (Range), μmol/L	76 (48-310)	118 (48-1421)	.100
Median Neutrophils (Range), $\times 10^9$/L	3.45 (2-10.8)	4.05 (1.6-11.9)	.419
Median Platelets (Range), $\times 10^9$/L	250 (146-386)	205 (56-405)	.427
Hemoglobin, g/dL	10.7 (7-14.7)	10.6 (7.4-16.1)	.258
Paraprotein, g/L	8.9 (1.5-55)	15.7 (1.6-51.4)	.920

Abbreviation: ALC-29 = absolute lymphocyte count at day 29 after chemotherapy.

Analysis of Day 29 ALC and OS

At the time of the analysis, 58% (22 of 38) of the patients had died; all patients died of MM. The choice of ALC-29 $\geq 0.8 \times 10^9$/L as the cutoff point was supported by the data because it yielded the greatest difference in survival, based on the χ^2 value ($\chi^2 = 8.4$; $P = .004$) analyzed at different cutoff points (0.5-1.5 $\times 10^9$/L), from the log-rank test. These different cutoff points were assessed because they fell between the 25% and 75% quartiles. The value of 0.8×10^9/L was also the median ALC-29 for the patient cohort. Patients with an ALC-29 $\geq 0.8 \times 10^9$/L (n = 16) experienced a superior median OS compared with patients with an