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Very high levels of Lactate Dehydrogenase at Diagnosis Predict Central Nervous System Relapse in Acute Promyelocytic Leukaemia

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With current treatments, > 90% of patients with acute promyelocytic leukaemia (APL) attain complete remission. However, 5-30% eventually relapse (Tallman 2007), and 3-5% relapse at extramedullary sites (Montesinos, *et al* 2009, Tallman 2007) most frequently the central nervous system (CNS) (Montesinos, *et al* 2009).

Patients with a white blood cell count (WBC) $> 10 \times 10^9/l$ have higher relapse rates (Sanz, *et al* 2004) including CNS relapse (de Botton, *et al* 2006). Therefore intrathecal (IT) prophylaxis in these patients has been advocated (Ades, *et al* 2006). As approximately 30% of APL patients present with a WBC $> 10 \times 10^9/l$ (Sanz, *et al* 2004), adopting this approach would lead to excessive unnecessary treatment. Other risks for CNS involvement are older age (de Botton, *et al* 2006), differentiation syndrome (Ko, *et al* 1999), CNS haemorrhage during induction and elevated baseline lactate dehydrogenase (LDH) (Montesinos, *et al* 2009). Whether any of these factors reliably identifies patients at risk for CNS involvement is unknown. Our aim was to identify patients that may benefit most from IT prophylaxis.

We reviewed 201 APL patients treated at the University of Texas MD Anderson Cancer Center (MDACC) between 1996 and 2013. Patients provided informed consent for treatment in clinical trials approved by the Institutional Review Board (IRB). Separate IRB approval was obtained for retrospective chart review. Patients were risk-stratified on the basis of WBC and platelet values: high- (WBC $> 10 \times 10^9/l$), low- (WBC $< 10 \times 10^9/l$ and platelet count $> 40 \times 10^9/l$) and intermediate- risk (WBC $< 10 \times 10^9/l$ and platelet count $< 40 \times 10^9/l$).

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Symptoms of CNS involvement with demonstration of blasts in the cerebrospinal fluid (CSF) was required for diagnosis of leptomeningeal disease. None received IT prophylaxis.

Patient characteristics were summarized using frequencies (percentages) for categorical and median and range for continuous variables. To detect variables predictive of CNS disease, we used multivariate logistic regression with stepwise variable selection. Variables were kept in the model if they were significant at a *P* value of 0.05. The $\text{Exp}(\beta)$ was used to estimate the odds-ratio (OR) and determine 95% confidence intervals (CI). To determine the optimal LDH cutoff at diagnosis that predicted CNS leukaemia we applied receiver operator characteristic (ROC) analysis. Statistical analyses were performed using the SPSS software (version 21, SPSS Inc., Chicago, IL).

Of 196 patients with APL treated at MDACC between 1996 and 2013 and alive after induction, 16 patients (8%) underwent later CSF analyses; CNS leukaemia blasts were detected in 8 patients (4%) at a median of 21 months from diagnosis (range 4 to 115).

Of seven patients with CNS disease in whom WBC and platelet counts at diagnosis were available, 5 (71%) had high-risk scores. In comparison, only 48 of 170 patients (28%) without CNS relapse had high-risk scores ($\text{WBC} > 10 \times 10^9/\text{l}$, $P = 0.03$).

Patients with CNS involvement had higher LDH at diagnosis, and higher numbers of promyelocytes in the bone marrow, but were similar for all other baseline characteristics tested (Table I, supplementary table 1). The induction protocol of patients with subsequent CNS disease included all trans retinoic acid (ATRA, $N = 8$), arsenic trioxide ($N = 6$) anthracyclines ($N = 5$) and cytarabine ($N = 1$). All responded and achieved complete remission prior to CNS relapse. The median time to CNS relapse was 21 months (range: 4 - 115); CNS disease was the site of first relapse in 3 patients.

Four patients relapsed in CNS and bone marrow (BM) and 4 had isolated CNS relapse. In addition to systemic chemotherapy, 7/8 patients received IT chemotherapy, typically combinations of steroids and alternating IT injections of methotrexate / cytarabine. These patients received a median of 8 IT treatments (range 3 to 43). After a median of 5 IT treatments, CSF cleared in five patients. One patient received emergent brain radiation and died soon thereafter with rapid neurological decline.

As continuous variables, LDH and WBC at diagnosis had minor power to predict CNS involvement. ROC analysis, indicated that a LDH cutoff level of 3000 iu/l level at diagnosis had sensitivity of 0.8 and specificity of 0.974 (Figure 1). LDH level at diagnosis was available in 156 patients; 11 patients had $\text{LDH} > 3000 \text{ iu/l}$, 4 of whom had documented CNS involvement. Only one patient with subsequent CNS relapse had $\text{LDH} < 3000 \text{ iu/l}$ at diagnosis ($\text{LDH} = 712 \text{ iu/l}$). The OR of $\text{LDH} > 3000 \text{ iu/l}$ for predicting CNS disease was 85 (95% CI: 8 - 865). In comparison, OR for $\text{WBC} > 10 \times 10^9/\text{l}$ was 6.1 (95% CI: 1 - 32). In multivariate analysis using LDH, WBC and BM blast percentages, only LDH remained predictive.

Even in patients with a high-risk score, the risk/benefit ratio for IT prophylaxis remains too high. In our study 10.2 patients would have received unnecessary treatment for any potential

benefit if all 56 with $WBC > 10 \times 10^9/l$ had been treated. Furthermore, two with CNS relapse had $WBC < 10 \times 10^9/l$ and would be missed. Finding a cluster of patients with elevated LDH provides a superior cutoff. If the 11 patients with $LDH > 3000 \text{ iu/l}$ at diagnosis were treated, only 1.75 patients would have received IT treatment for each patient with potential benefit, and only one patient $< 3000 \text{ iu/l}$ would be missed.

LDH is an independent risk factor for CNS involvement across the haematological malignancies (Cortes, *et al* 1995). In our series, very high LDH was the strongest predictor for CNS relapse, independent of disease burden as reflected by peripheral WBC or percentage of BM promyelocytes.

LDH catalyses the conversion of pyruvate to lactate. Under normal oxygen tension, cells utilize oxidative phosphorylation and conversion of pyruvate to lactate is minimal. However, under hypoxia, cells do not utilize oxidative phosphorylation and lactate produced by LDH induces cellular proliferation (Irani, *et al* 1997). Because high plasma LDH correlates with high intracellular LDH (Ho, *et al* 1984), it is likely that APL cells with a very high LDH concentration are particularly adjusted to survive in the brain, a relatively hypoxic tissue (Evans, *et al* 2004).

In conclusion, $LDH > 3000 \text{ iu/l}$ predicts CNS relapse. Therefore, IT prophylaxis should be considered in patients with very high LDH levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Receiver-operating characteristic curve analysis and the corresponding area under the curve (AUC) of lactate dehydrogenase (LDH) levels at diagnosis for detecting central nervous system relapse in patients with acute promyelocytic leukaemia. The sensitivity and specificity of putative cutoffs in LDH at diagnosis is depicted. The AUC was 0.867, $P = 0.005$.

Table 1

Baseline characteristics of the study population

	non-relapsed patients (N= 161)	Relapsed patients (N = 35)	CNS involvement (N = 8)	no CNS involvement (N = 27)	P value
Median age (range), years	46 (14 to 81)	45 (28 to 79)	45 (28 to 79)	47 (18 to 67)	0.8
Sex n (%)					0.2
Male	76 (47)	6 (75)	6 (75)	15 (56)	
Female	85 (53)	2 (25)	2 (25)	12 (44)	
Laboratory values, median (range)					
WBC count, $\times 10^9/l$	2.3 (0.4 - 103)	43 (1.7 - 128)	43 (1.7 - 128)	21 (0.6 - 131)	0.01
Haemoglobin, g/l	91 (50 - 540)	82 (52 - 118)	82 (52 - 118)	93 (38 - 121)	0.7
Platelet count, $\times 10^9/l$	36 (4 - 261)	21 (6 - 71)	21 (6 - 71)	27 (10 - 58)	0.2
LDH, iu/l	800 (246 - 8660)	3639 (712 - 9769)	3639 (712 - 9769)	686 (249 - 2685)	0.02
Median BM blasts (range), %	3 (0 - 91)	15 (0 - 65)	15 (0 - 65)	6 (0 - 90)	0.5
Median BM promyelocytes (range), %	68 (0 - 96)	80 (26 - 91)	80 (26 - 91)	71 (0 - 90)	0.05
Risk score n (%)					
Low	56 (36)			1 (7)	0.02
Intermediate	57 (36)	2 (29)	2 (29)	8 (57)	
High	43 (28)	5 (71)	5 (71)	5 (36)	

CNS, central nervous system; WBC, white blood cell; LDH, lactate dehydrogenase; BM, bone marrow.