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ORIGINAL ARTICLE

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Safety of lumbar puncture for adults with acute leukemia and restrictive prophylactic platelet transfusion

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Abstract No data exist on the trigger for platelet transfusions in adult thrombocytopenic patients with acute leukemia undergoing lumbar puncture (LP). We reviewed the records of 66 patients with acute leukemia (median age 38 years, range 18–68) who have been treated in our institution for 6 years. A total of 195 LPs were performed. No serious hemorrhagic complications occurred, but there was a significant trend towards a higher percentage of traumatic procedures, defined as the occurrence of >500 erythrocytes per high-power field, in patients with lowest platelet counts ($p<0.005$). Although not associated with serious clinical bleeding events in this study, the increased occurrence of traumatic procedures may indicate an increased risk for more serious hemorrhagic complications, implying a trigger not lower than 20×10^9/L for prophylactic transfusions of platelets in adult patients with acute leukemia undergoing LP.

Keywords Acute leukemia · Lumbar puncture · Safety · Platelets · Transfusion

Introduction

Platelet transfusions are increasingly demanded in patients with hematologic malignancies. However, the recruitment of platelet donors is difficult, and repeated use of platelet transfusions is associated with increasing risk of transfusion reactions, transfusion-transmitted diseases, alloimmunization, and considerable costs. Thus, current guidelines recommend restrictive prophylactic strategies [10].

Multiple randomized trials support a threshold of 10×10^9/L, above which prophylactic transfusion is considered unnecessary in the absence of hemorrhage in stable, non-febrile patients with acute leukemia [5, 8]. Nevertheless, there is still uncertainty about the lower level of platelet count that is safe in thrombocytopenic patients with leukemia undergoing invasive procedures, e.g., diagnostic or therapeutic lumbar punctures (LP) [10]. Whereas a recent large retrospective review and a follow-up study showed that platelet counts as low as 10×10^9/L may be sufficient for safe LP in children with lymphoblastic leukemia [6, 7], firm data in adult patients with acute leukemia are lacking. Based on the occurrence of severe bleeding complications following LP in patients with platelet counts below 20×10^9/L, a platelet count of 20×10^9/L was recommended as threshold for platelet transfusions prior to LP in adults [1, 3]. However, no systematic study has tested this recommendation so far.

In our institution, restrictive strategies for prophylactic platelet transfusions are used [4] and the recommendation of transfusing platelets only when counts are lower than 20×10^9/L prior to LP has long been adopted. Herein we describe our experience in using this strategy in adult patients with acute leukemia undergoing LP.

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Patients and methods

Study design and patient population

We retrospectively analyzed the medical charts of patients with acute leukemia who were treated from January 1995 to February 2001 at the University Hospital Zurich, Switzerland, and underwent one or more therapeutic or prophylactic lumbar puncture(s) (LP). To be included in the analysis, the patient had to be at least 18 years old, and coverage of a follow-up period of at least 14 days after the LP was required. The basic characteristics of the patients are summarized in Table 1. We recorded platelet counts on the morning of LP, as well as the 1-h platelet count after transfusion, in case transfusion was required. Results were available for high-powered field (HPF) microscopic examinations of cerebrospinal fluid (CSF). A traumatic LP was defined if >500 red blood cells were present

per HPF. Clinical events that were potentially attributed to LP procedures and all neurologic, infectious, or hemorrhagic events that occurred within 14 days after LP were noted. Headache, nausea, irritability or somnolence, and low back pain were excluded.

Statistics

Results are presented as median (range). Nonparametric statistical tests were used throughout. Continuous variables between groups were compared using a two-tailed Mann-Whitney U test or a Kruskal-Wallis one-way analysis of variance with Dunn's Multiple Comparisons Tests. Discontinuous variables were analyzed by the Chi-squared test for trend. The 95% confidence intervals (CIs) for the probability of serious hemorrhagic complications at each level of platelet counts were defined using the exact confidence limits based on a binominal distribution; for the upper bound of the confidence interval, the formula $p=1–0.025^{(1/n)}$ was used [2]. Statistical calculations were performed using InStat version 3.05 (GraphPad, San Diego, CA, USA). $p<0.05$ was considered significant.

Results and discussion

We retrospectively identified 66 patients who were treated with intensive chemotherapy regimens and/or bone marrow transplantation for hematologic malignancies and met our inclusion criteria; Table 1 summarizes their basic characteristics. These patients underwent a total of 195 LPs (24 diagnostic, 171 therapeutic, Table 2). Results from CSF examinations were available from all but 16 LPs, which were nevertheless included in the analysis since the patients were assessable for potential complications. On the morning of the day of the scheduled LP, 37 patients had platelet counts below 20×10^9/L and received platelets according to the institution's transfusion criteria. Afterwards, the effect of transfusion was verified with a 1-h post-transfusion count, and the LP was performed only when platelet counts increased to values higher than 20×10^9/L. The platelet counts at the time of LP are shown in Table 2. A traumatic puncture, defined as the occurrence of >500 erythrocytes/HPF, was noted after 14 procedures (6,7%). There was a significant trend towards higher percentage of traumatic punctures in patients with lower platelet counts (Chi-square test for trend: 9.46, $p<0.005$). Table 3 shows the characteristics of the patients with platelet counts $<25\times10^9$/L at the time of LP. In none of the 195 procedures, however, occurred more serious bleeding events or other adverse sequelae.

A total of five adverse events (meningoencephalitis, leukencephalopathy, meningism, tonic-clonic seizure, and transient ischemic attack) that were considered potentially related to LP procedures were found. All events occurred after a therapeutic, non-traumatic LP and did not appear to be associated with patients with lower platelet counts (range of platelet counts at LP: $23–247\times10^9$/L).There was no evidence for underlying bleeding in any of these patients, both by radiological means and by repeated LP, which were all non-hemorrhagic. Thus, given the fact that there was no clinical or laboratory evidence for hemorrhage, these adverse events were not considered related to thrombocytopenia-associated bleeding and were not included in the estimation of probability of serious bleeding complications following LP. A more likely explanation for the adverse events was local irritation by instilled chemotherapy in cases with meningeal symptoms occur-

Table 1 Basic characteristic of 66 patients with acute leukemia undergoing lumbar puncture

Demographics	
Number of patients (female/male)	66 (29/37)
Age, years (range)	38 (18–68)
Diagnosis	
Acute myeloid leukemia AML total (n)	28
AML M1	2
AML M2	5
AML M4	13
AML M5	7
AML M6	1
Acute lymphoblastic leukemia (n)	38

Table 2 Clinical conditions at time of lumbar punctures and results from cerebrospinal fluid analysis

	Platelet count at LP				
	All	$20–30\times10^9$/L	$31–50\times10^9$/L	$51–100\times10^9$/L	$>101\times10^9$/L
Number of LPs performed (n)	195	35	40	43	77
Diagnostic/therapeutic (n)	24/171	5/30	7/33	4/39	8/69
Patients requiring transfusion (n)*	37	16	10	11	0
Platelet counts at LP ($x10^9$/L)**	32 (20–893)	24.5 (20–30)	37.5 (31–42)	60 (51–85)	227 (102–893)
Hemostatic parameter (INR)	1.1 (0.8–1.7)	1.1 (0.9–1.4)	1.2 (0.9–1.7)	1.1 (0.8–1.3)	1 (0–8-1.4)
Temperature (°C)	37.8 (36.2–39.9)	37.9 (36.4–39.5)	38.3 (36.9–39.9)	37.8 (37–39.4)	37 (36.2–39.6)
Cerebrospinal fluid analysis, number of LPs with					
Blast cells	15	2	4	4	5
Erythrocytes >500 HPF	14	6	4	3	1

Quantitative variables are expressed as median (range); qualitative variables are expressed as n. *HPF* high-power field.
* patients received platelet transfusions when platelet counts were below 20×10^9/L on the day of LP; platelet counts were re-determined 1 h after transfusion
** shown is last platelet count measurement prior to LP, i.e., morning value in patients who did not receive platelet transfusions on the day of LP or 1h post-transfusion counts in patients who received platelet transfusions

Table 3 Overview of 17 patients with platelet counts <25×10^9/L at LP

Patients	Age (y)	Gender	Platelet count at LP (x10^9/L)*	Substitution**	Hemorrhagic LP	Side effects
1.	50	M	20	–	–	–
2.	42	F	20	–	–	–
3.	42	F	20	–	+	–
4.	55	F	20	+	–	–
5.	38	M	21	–	–	–
6.	28	M	21	+	+	–
7.	65	F	21	+	–	–
8.	48	F	21	+	–	–
9.	25	M	22	–	–	–
10.	44	M	22	+	–	–
11.	21	F	23	–	–	–
12.	28	M	23	–	–	–
13.	42	F	23	–	–	–
14.	18	M	23	+	–	Meningoencephalitis
15.	48	F	24	-	–	–
16.	67	M	24	+	+	–
17.	18	M	24	+	–	–

*Shown is last platelet count measurement prior to LP, i.e., morning value in patients who did not receive platelet transfusions on the day of LP or 1-h post-transfusion counts in patients who received platelet transfusions
**Denotes platelet transfusion on day of LP

Table 4 Platelet counts, number of lumbar punctures (LPs) performed, and the estimated probability of serious complications

Platelet count (×10^9/L)	No. of LPs	95% CI for complications (%)
20–30	35	0.00–10.0
30–50	40	0.00–8.81
50–100	43	0.00–8.22
>100	77	0.00–4.68
Total	195	0.00–1.87

CI confidence interval

ring shortly after LP, as well as in the patient with radiological evidence for leukencephalopathy. The pathogenesis of the transient-ischemic attack or the meningoencephalitic symptoms that occurred over 3 weeks after the LP remained unclear, but a causal relationship to the LP procedure was questionable.

Therefore, we did not observe any serious bleeding event in our study population. However, a major limitation of the present study is its limited sample size, which precludes any firm conclusion about the precise risk for serious bleeding events. To take this limitation into account, we performed an additional statistical analysis to determine the statistical probability of serious hemorrhagic complications based on our data. As shown in Table 4, the 95% confidence interval is rather wide, reflective of the relatively limited number of procedures performed.

There is still controversy about the trigger for platelet transfusions in adult patients with acute leukemia [10]. Although a recent large study showed that platelet counts as low as 10×10^9/L seem to be safe in children with acute leukemia [6, 7] these results may not be transferable to adults, in which LPs may be more difficult to perform and therefore more prone to complications. Defining firm criteria for the trigger of prophylactic platelet transfusions in thrombocytopenic adults with leukemia is of considerable interest for medical and economic reasons.

Our results suggest that the trigger for platelet transfusions when performing LPs may be as low as 20×10^9/L in adult patients with acute leukemia. Caveats have to be included, however. First, although this is so far the largest study investigating the trigger for platelet transfusion in this patient population, the actual number of procedures is still relatively small, and statistical means are necessary to more adequately determine the probability of serious complications. And second, there was a significant trend towards a higher percentage of procedures with hemorrhagic CSF in patients with lower platelet counts. Although such procedures may not account as serious hemorrhagic complication per se, a traumatic LP was shown to be associated with a higher incidence of severe complications in non-thrombocytopenic control patients and patients with heparin therapy [9], and it is conceivable to assume that this could also be true for thrombocytopenic patients. If true, our data would suggest that patients with the lowest platelet counts at the time of the LP might be at a slightly higher risk for serious hemorrhagic complications. Together with the previous observation of severe bleeding complications following LP in adult patients with platelet counts below 20×10^9/L [1, 3], the present study supports a trigger not lower than 20×10^9/L for prophylactic platelet transfusion in adult patients with acute leukemia in whom a diagnostic or therapeutic LP is to be performed.

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