Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study

Mathilde Hunault-Berger,[1] Patrice Chevallier,[2] Martine Delain,[3] Claude-Eric Bulabois,[4] Serge Bologna,[5] Marc Bernard,[6] Ingrid Lafon,[7] Jérome Cornillon,[8] Abdallah Maakaroun,[3] Alexandra Tizon,[1] Bruno Padrazzi,[9] Norbert Ifrah,[1] and Yves Gruel[3] for the GOELAMS (Groupe Ouest-Est des Leucémies Aiguës et Maladies du Sang)

Hematology Departments of Angers,[1] Nantes,[2] Tours,[3] Grenoble,[4] Nancy,[5] Rennes,[6] Dijon,[7] Saint Etienne[8] and LFB-Paris,[9] France

ABSTRACT

Background

The effects of L-asparaginase on hemostasis during induction chemotherapy are less defined in adults than in children. We, therefore, studied the effects of L-asparaginase in adult patients.

Design and Methods

This was a retrospective analysis of 214 patients treated with L-asparaginase (7500 IU/m^2 x 6) for acute lymphoblastic leukemia or lymphoblastic lymphoma. Between day 1 of the induction course and discharge, clinical events, and biological and therapeutic modifications were reviewed.

Results

Antithrombin and fibrinogen levels were lower than 60% and 1 g/L in 71% and 73% of patients, respectively. Twenty thromboses occurred in 9.3% of the patients; these patients had a median antithrombin level of 53% (range, 21-111) at the time of the event. Forty-two episodes of bleeding occurred in 31 patients with a median fibrinogen level of 1.3 g/L. Infusions of L-asparaginase were reduced or delayed in 64% of patients due to low fibrinogen and/or antithrombin levels. Fresh-frozen plasma, antithrombin and fibrinogen were infused in 31%, 41% and 52% of patients, respectively. The mean antithrombin and fibrinogen levels increased from 61% to 88% and from 1 to 1.4 g/L after infusion of antithrombin or fibrinogen respectively, while both levels remained unchanged after the infusion of fresh-frozen plasma. In patients who received antithrombin concentrates L-asparaginase injections were less frequently omitted or delayed (53% *vs.* 72%, p=0.005), the rate of thrombosis was lower (4.8% *vs.* 12.2%, p=0.04) and the disease-free survival was also reduced (p=0.05).

Conclusions

This retrospective study suggests that antithrombin concentrates may have a beneficial effect on the outcome of adults treated for acute lymphoblastic leukemia with L-asparaginase; prospective studies are essential to confirm this hypothesis.

Key words: L-asparaginase, acute lymphoblastic leukemia, antithrombin, fibrinogen.

Citation: Hunault-Berger M, Chevallier P, Delain M, Bulabois C-E, Bologna S, Bernard M, Lafon I, Cornillon J, Maakaroun A, Tizon A, Padrazzi B, Ifrah N, and Gruel Y for the GOELAMS (Groupe Ouest-Est des Leucémies Aiguës et Maladies du Sang). Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study. Haematologica 2008; 93:1488-1494.
doi: 10.3324/haematol.12948

Acknowledgments: the authors thank Ms Anne-Cécile Jaffry for her help in the statistical analysis of the data and Dr Tony Waegemans for helpful discussions.

Manuscript received February 21, 2008. Revised version arrived June 10, 2008. Manuscript accepted June 23, 2008.

Correspondence:
Yves Gruel, Service d'Hématologie-Hémostase, Hôpital Trousseau, 37044 Tours Cedex, France.
E-mail: gruel@med.univ-tours.fr

Introduction

L-asparaginase is an enzyme whose therapeutic effect in acute lymphoblastic leukemia (ALL) has been well documented in children[1,2] but its usefulness remains discussed in adults.[3,4] This drug induces a relative asparagine deficiency that leads to the death of human lymphoblasts. L-asparaginase has, however, also been shown to be toxic to the liver, pancreas, central nervous system (CNS) and kidneys, particularly when derived from *E. coli*. Furthermore, it has been reported that treatment with L-asparaginase causes widespread impairment of hemostasis by inhibiting biosynthesis of hepatic L-asparagine-dependent proteins. Plasma antithrombin (AT) and fibrinogen (Fg) levels decrease more significantly than those of any other hemostatic protein[5] and this effect may be associated with an increased tendency to bleeding or thrombosis.

These hemostatic modifications induced by L-asparaginase are relatively rare and mild in children, but their incidence has not yet been well evaluated in adults. Moreover, the ways of preventing or treating these coagulation defects and their consequences are poorly defined. We, therefore, performed a multicenter retrospective study to address these issues, analyzing the data from 214 adult patients with ALL or T-lymphoblastic lymphoma (T-LBL) who had received induction therapy including six infusions of L-asparaginase.

Design and Methods

Patients

Two hundred and fourteen patients aged from 15 to 59 years old treated for non-Burkitt's type ALL or T-LBL in 22 Intensive Care Hematology centers in France were included in the CAPELAL study. Four were subsequently excluded because they had not received injections of L-asparaginase during the induction course. With the agreement of the Ethics Committee in Angers, 3 months before the study, a letter was sent to living patients to obtain permission to review their records for this retrospective analysis. All patients had been included between September 1994 and December 1998 in either the GOELAL02 trial[6] (n= 191/198) or the T-LBL/ALL GOELAL02 trial[7] (n=23/30) depending on initial criteria comprising age, leukocytosis, percentage of bone marrow involvement, immunophenotype, poor-prognosis cytogenetic abnormalities and/or failure to achieve complete remission after the first induction course. Consolidation courses were less intensive for patients included in the T-LBL/ALL GOELAL02 trial. Risk factors for thrombosis such as age, personal and familial history of thrombosis, use of contraceptive drugs, symptomatic thromboses and previous significant bleeding events, were recorded for each patient.

Chemotherapy regimen and supportive hemostatic treatment

Induction therapy was based on the BFM regimen[8] and consisted of weekly intravenous administration of vincristine (2 mg/injection) and idarubicin (5 mg/m^2/injection) on days 1, 8, 15, and 22 with six doses of intravenous *Escherichia coli* L-asparaginase (7500 IU/m^2 on days 10, 13, 16, 19, 22 and 25) in addition to 3 weeks of daily steroids (40/mg/m^2/day). The fourth injection of vincristine was replaced by teniposide (100 mg/m^2) in cases of poor neurological tolerance. *Erwiniase* was used in cases of anaphylactic reaction (7500 IU/injection).

Blood-derived products, i.e. fresh-frozen plasma (FFP), Fg (Clottagen®, LFB, Les Ulis, France) and AT (Aclotine®, LFB) concentrates were recommended to maintain Fg and AT levels at >1 g/L and 60%, respectively. Alternatively, injections of L-asparaginase were delayed for 48 hours if no blood-derived products were administered. Platelets were transfused when counts were < 20×10^9/L and antithrombotic prophylaxis was prescribed in accordance with institutional guidelines. The most frequently applied protocol (in 75 patients) was based on the use of heparin (100 IU/kg/day) administered by intravenous infusion, which was stopped if the platelet count decreased below 20×10^9/L.

Clinical and laboratory parameters

Thrombotic or bleeding events occurring between the first injection of L-asparaginase and the patient's discharge at the end of induction therapy were recorded. Hemoglobin (Hb) levels, white blood cell and platelet counts, Fg level (assessed by the von Clauss assay) and AT level (evaluated by a chromogenic assay), measured from diagnosis to the end of the induction regimen, were analyzed. The diagnosis of disseminated intravascular coagulation was based on the ISTH subcommittee criteria.[9] To evaluate changes in AT and Fg levels after treatment with L-asparaginase, AT and Fg values measured before administration of any blood-derived product were analyzed. The efficacy of FFP, AT and Fg concentrates on plasma Fg and AT levels was evaluated by comparing values measured in the 24 hours before infusion of these blood-derived products to the values measured the following day.

Statistical analysis

Differences between groups were analyzed by the χ^2 test or Mann-Whitney U-test when appropriate. Odds ratios (OR) and confidence intervals (CI) were calculated with a logistic regression model. Overall survival and disease-free survival were analyzed by the Kaplan-Meier method, and differences in survival times were assessed by the log-rank test. SPSS software version 10.1.3 for Windows (SPSS Inc. Chicago, IL, USA) was used for these analyses.

Results

Patients' pretreatment characteristics

The median age of the patients was 32 years (range, 15-59) and 60% were male. At diagnosis, 24% of the patients had white blood cell counts ≥ 30×10^9/L and 7% had white cell counts ≥100×10^9/L. The median hemoglobin concentration was 97 g/L (range, 59-159), and

the median platelet count was 62×10^9/L (range, 4-610). Disseminated intravascular coagulation was present in 7.5% of patients at diagnosis. None of the patients had a bleeding diathesis, while 5.6% and 8.4% of patients reported a personal or familial history of thrombosis, respectively. Combined oral contraceptives were stopped before initiation of induction therapy in all but 14 patients (4 with thrombosis and 10 without) and norpregnane derivatives (nomegestrol) were administered. Central venous access was used in all patients, but a port chamber was used in only three. One patient had previously been diagnosed as having hereditary protein S deficiency.

Treatment with L-asparaginase

Fifty-nine percent of patients received the six planned injections of *Escherichia coli* L-asparaginase, although injections were delayed at least once in 22% of cases. The number of injections of L-asparaginase was reduced in 41% of patients, to five (18%), four (8%), three (8%), two (5%) or one (2%) administrations. The most frequent explanation for withdrawal or delayed treatment with L-asparaginase was the presence of coagulation abnormalities, particularly Fg or AT deficiency (Table 1). In addition, five patients were treated with asparaginase from *Erwinia* because of allergic reactions.

Changes in fibrinogen and antithrombin levels after injection of L-asparaginase and effects of blood-derived products

Fg and AT levels were measured 4098 times (20 times/patient) and 1718 times (8 times/patient), respectively, between day 1 and discharge. AT levels did not decrease in the first 10 days of induction chemotherapy and before treatment with L-asparaginase (Figure 1). The median AT level then decreased from 120% (before the first infusion of L-asparaginase) to 59% at the time of the fourth infusion. In addition, AT levels lower than 60% were found in approximately half of patients at the fourth infusion. Fg levels decreased from 2.9 g/L at diagnosis to 1.9 g/L before the first infusion of L-asparaginase, although disseminated intravascular coagulation, which was present in 7.5% of patients, had been corrected (Figure 2). Fg levels then continued to decrease after the first 10 days of induction therapy, reaching a median value of 1.1 g/L at the time of the fourth infusion of L-asparaginase. Finally, Fg levels were lower than 0.8g/L at the time of the fifth infusion of L-asparaginase in 31% of patients evaluated.

In accordance with protocol recommendations and/or institutional guidelines, FFP, Fg and AT concentrates were infused at median doses of 5.4 mL/kg, 0.03g/kg and 31 IU/kg per infusion, respectively, in 31%, 52% and 41% of patients. Nineteen percent of patients did not, therefore, receive any replacement therapy. On the other hand, at least two of these blood-derived products were infused in 39% of cases.

Table 1. Reasons for reducing the number of injections of L-asparaginase or delaying treatment.

	Delay n=47 (22%)	*Reduced number of injections n=89 (41%)*
Low AT level	4	1
Low Fg level	11	16
Other coagulation abnormalities	7	14
Thrombosis	-	7
Hepatotoxicity	4	15
Pancreatic reaction	-	11
Infectious complication	3	4
Anaphylactic reaction	2	1
Logistic reason	16	14
Miscellaneous	-	6

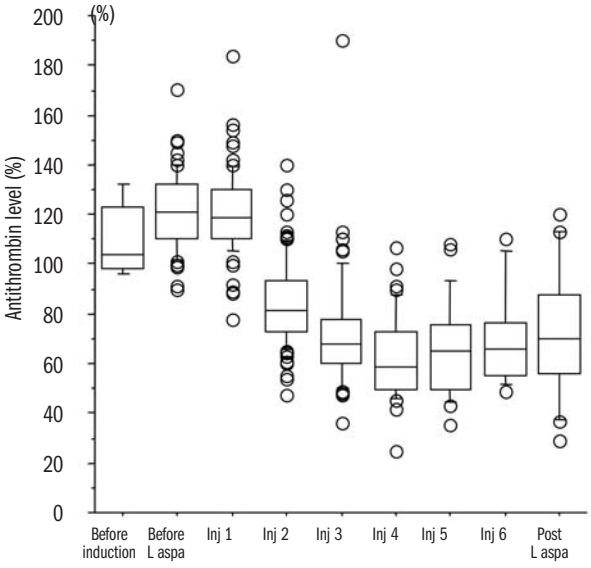

Figure 1. Changes in antithrombin levels during induction chemotherapy for acute lymphoblastic leukemia without any infusion of fresh-frozen plasma or antithrombin concentrates.

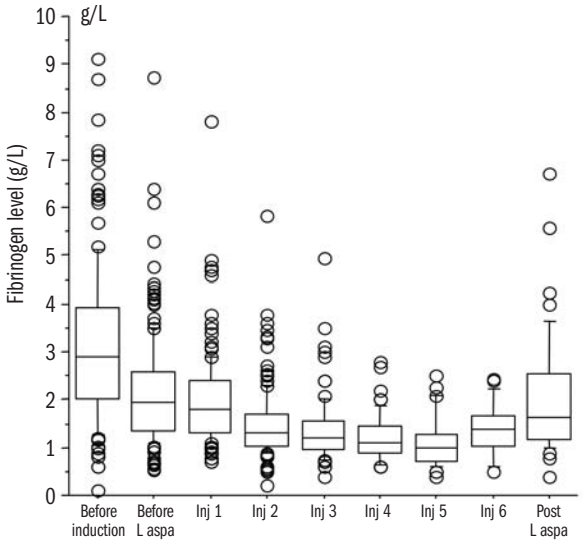

Figure 2. Changes in fibrinogen levels during induction chemotherapy for acute lymphoblastic leukemia without any infusion of fresh-frozen plasma or fibrinogen concentrates.

Changes in AT and Fg levels before and after infusion of blood-derived products are shown in Figure 3. Infusion of AT concentrate was followed by a significant increase in AT levels (from 61 ± 16% to 88%±23%, $p<0.0001$); the levels were not changed by FFP administration. Infusion of AT concentrates also reduced the percentage of patients with AT levels <60% from 45.2 to 10.8%, whereas FFP had no effect. Fg levels significantly increased (from 1.0±0.3 g/L to 1.4±0.45 g/L, $p<0.0001$) after infusion of Fg concentrates, but they remained unchanged after FFP was administered (1.0±0.4 *vs.* 1.1±0.5 g/L). The number of doses of L-asparaginase injected was similar in patients who received at least one blood-derived product (n=173, 5.2 injections/patient) or none (n=41 patients, 4.9 injections/patient). However, treatment with L-asparaginase was less frequently modified (with either a delay or reduced number of injections) in patients who had received preventive injections of AT than in the others (53% *vs.* 72%, OR 0.44, 95% CI 0.25-0.79; $p=0.005$).

Thrombotic events

Twenty-one thrombotic events (9.8%) were diagnosed during the induction phase. Bilateral distal thrombosis occurred in one patient without disseminated intravascular coagulation or AT deficiency 3 days after diagnosis, and thus before administration of L-asparaginase. Since the aim of this study was to evaluate the effects of L-asparaginase in adults, this event was not taken into account in our analysis. The 20 thrombotic events (in 9.3% of the patients, 95%CI 5.4-13.2%) occurred from 2 to 35 days after the first injection of L-asparaginase (Table 2), after a median of four injections of L-asparaginase (range, 1-6). Treatment with L-asparaginase was stopped because of thrombotic events in 10 patients. It was withdrawn prior to the event for other reasons in three patients and was continued despite thrombosis in four cases. In three patients, all six injections of L-asparaginase had been given when thrombosis was diagnosed. These thrombotic events comprised cerebral vein thrombosis (n=5, 25%), pulmonary embolism (n=3, 15%), and deep vein thrombosis in the upper (n=5, 25%) or lower (n=7, 35%) limbs. The diagnosis of thrombosis was confirmed by echo-Doppler (n=10), computed tomography-scan (n=3), magnetic resonance imaging (n=2), angioscan (n=1), or ventilation-perfusion lung scan (n=1) in all patients except three for whom further investigations were impossible due to their critical clinical condition. Thrombotic events were treated with unfractionated heparin (n=13) or low molecular weight heparin (n = 5). Two patients with CNS thrombosis did not receive heparin. Nine patients (including eight with AT levels lower than 60%) also received AT concentrates. Two other patients did not receive AT concentrates despite low levels at the time of thrombosis (47% and 35%).

The risk factors for thrombosis recorded in these patients are presented in Table 2. Recent treatment with oral contraceptives was more frequent in women with thrombosis than in those without (4/10 *vs.* 10/75, OR 4.33; 95% CI 1.04-18.1; $p=0.03$). No other significant difference was observed, and the total number of injections of L-asparaginase administered to patients

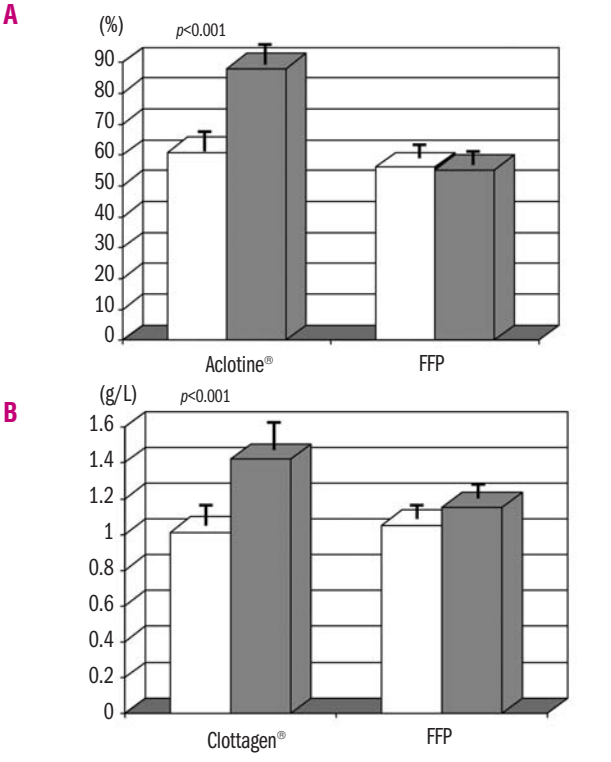

Figure 3. Changes in antithrombin (A) and fibrinogen levels (B) before and after infusion of blood-derived products.

Table 2. Characteristics of the patients with and without thrombosis.

	Thrombosis n=20	*No thrombosis n=194*	*p*
Familial thrombophilia	1	17	
Previous thrombosis	2	13	
Median age (range)	38 (16-52)	30 (15-59)	
Gender (female/male)	10/10	75/119	
Oral contraceptives	4/10 (40%)	10/75 (13%)	0.03
Body mass index (kg/m^2)	24 (20-41)	23 (15-45)	
Smoking	4 (20%)	71 (37%)	
ALL/T-lymphoblastic lymphoma	18/2	173/21	
Disseminated intravascular coagulation	2 (10%)	14/168 (7.8%)	
Mean number of injections of L-asparaginase (range)	5 (1-6)	6 (1-8)	
AT nadir; median (range)	48% (34-110)	51% (13-120)	
AT <60%	12/17 (70%)	98/139 (70%)	
Fg nadir, median g/L (range)	0.61 (0.21-1.2)	0.8 (0.2-4.94)	
Fg < 0.5g/L	4 (20%)	14 (7.3%)	
Low doses of heparin	6 (30%)	79/192 (41%)	
FFP	5 (25%)	62 (32%)	
AT concentrates	10* (50%)	78 (40%)	
Fg concentrates	12 (60%)	99 (51%)	
Complete remission, %	85	89	
7-year overall survival, %	30	48	0.06
7 years disease-free survival, %	29	49	0.05

** four patients had received AT before thrombosis.*

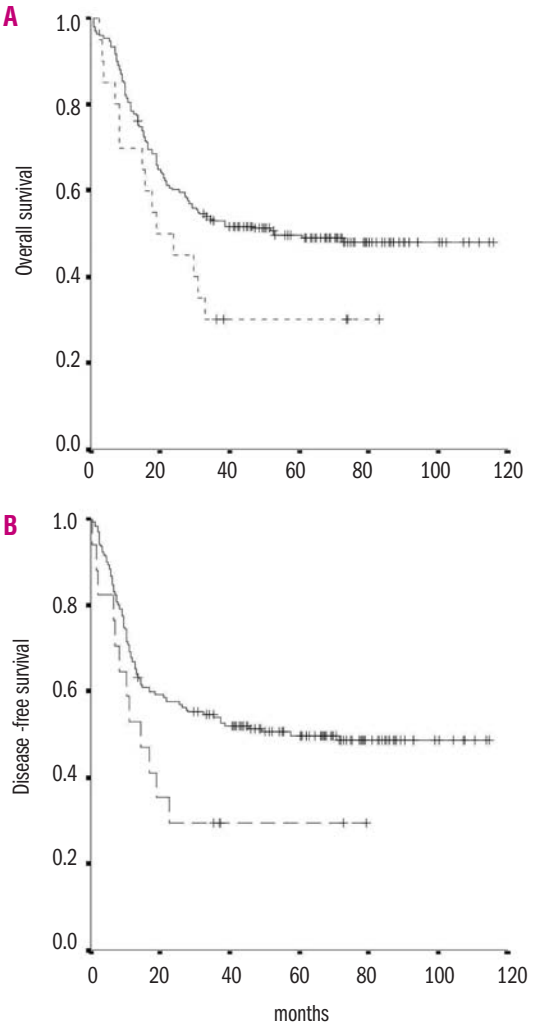

Figure 4. Kaplan-Meier survival curves in patients without and with thrombosis. (A) Overall survival (B) Disease-free survival.

with or without thrombosis was similar.

AT levels were measured at the time of the event or in the days before thrombosis in 18 patients and were lower than 60% in 11 cases (61%) (median value 48%; range, 21-120). Importantly, the rate of thrombosis was lower in patients who had received AT concentrates (4/83, 4.8%) than in those who had not (16/131, 12.2%, OR 0.39; 95%CI 0.11-1.02; p=0.04). However, the rate of thrombosis was similar in patients who had or had not received prophylactic anticoagulation (6/85 *vs.* 14/127), FFP (5/67 *vs.* 15/147), or Fg concentrate (12/111 *vs.* 8/103).

Hemorrhagic events

Forty-two bleeding events occurred between 1 to 45 days (median, 8 days) after the first infusion of L-asparaginase in 31 patients (14.5%, CI 95% 9.8-19.2). These events were epistaxis (n=24), central venous access bleeding (n=8), rectorrhagia (n=1), large hematomas (n=8), and hemorrhagic stroke (in one patient who also had cerebral vein thrombosis). Bleeding events were diagnosed after a mean number of 2.4 infusions of L-asparaginase (range, 1-6). Apart from the hemorrhagic stroke, none of the bleeding events was considered to be severe, and platelets, FFP, Fg or AT concentrates were administered in only a few instances (for 7, 5, 8, and 1 events, respectively). The hemorrhagic events were not associated with a higher frequency of disseminated intravascular coagulation, more frequent use of unfractionated heparin or low molecular weight heparin (32% *vs.* 44% of patients without bleeding), higher number of infusions of L-asparaginase or difference in platelet count or Fg nadir (median 55 *vs.* 58×10^9/L, 0.9 *vs.* 0.8 g/L, respectively). In addition, AT, Fg concentrates and FFP were administered equally in patients with and without bleeding. The mean number of red blood cell units transfused was higher in patients with hemorrhagic events (4.3 *vs.* 2.1) although the difference was not statistically significant.

Relationship between acute lymphoblastic leukemia outcome, and thrombosis and hemorrhage

The general outcomes of the patients in this study and their prognostic factors have already been reported.[6,7] The complete remission rate was similar in patients with and without thrombosis (Table 2). Despite none of the thrombotic events being fatal, the occurrence of thrombosis was associated with a reduced median overall survival (19 months *vs.* 53 months, p=0.06) and disease-free survival (14 months *vs.* 58 months, p=0.05) (Figure 4). This shorter survival time of patients with thrombosis was not related to any of the known prognostic factors for ALL, such as age, white cell count, or early achievement of complete response. Patients who had received five or six injections of L-asparaginase had a longer median overall survival (52 months *vs.* 31 months) and disease-free survival (70 months *vs.* 22 months) than those treated with four or fewer infusions, although the difference was not statistically significant. Finally, hemorrhagic events were not associated with any difference in patients' survival.

Discussion

The aims of this large retrospective study were to evaluate the effects of L-asparaginase on coagulation parameters in adult patients treated for ALL, and, specifically, to evaluate the consequences on Fg and AT levels. The clinical risks, i.e. bleeding and thrombosis, potentially associated with these changes in coagulation and the benefits of supportive treatment using blood-derived products were also evaluated. Blood coagulation abnormalities induced by the administration of *E-coli*-derived L-asparaginase during induction chemotherapy have been widely documented in children with ALL,[5,10-13] but little information is available for adult patients. L-asparaginase administered to 25 adults in induction chemotherapy including anthracycline, prednisone and vincristine was shown to induce significant decreases in Fg, AT, plasminogen, and α_2-antiplasmin, with the lowest levels measured after the last infusion of L-asparaginase.[14] Our study, involving a larger population of

patients confirmed this reduction in AT and Fg levels. Fg initially decreased from day 1 to day 10 while corticosteroids were administered and despite the correction of disseminated intravascular coagulation, which was diagnosed in 7.5% of patients (a rate similar to that previously described).[15] This decrease in plasma fibrinogen was then enhanced, reaching a median level of 1 g/L at the time of the fourth infusion of L-asparaginase. In addition, the median AT level decreased from 120% before administration of L-asparaginase to 59% at the time of the fourth infusion, with almost 50% of patients having AT levels below 60%. Despite the high frequencies of Fg and AT deficiency, the incidence of hemorrhagic and thromboembolic events was 14.5% and 9.3%, respectively. However, the use of retrospective records to evaluate the frequency of such events probably induced some bias in data collection and only clinically significant hemorrhages were recorded. Most of the hemorrhagic manifestations that occurred during induction therapy for ALL were mild, as previously reported.[16] On the other hand, no increase in the incidence of bleeding was observed in patients with Fg levels lower than 0.5 g/L. However, FFP and Fg concentrates were frequently infused and this possibly reduced the risk of hemorrhage. FFP and Fg concentrates were administered to 31% and 52% of patients, respectively, but Fg levels increased only after infusion of Clottagen®. FFP induced no significant changes, but this can be explained by the fact that relatively small amounts of plasma, i.e. 5.4 mL/kg, were infused, whereas 20 mL/kg are usually necessary to increase Fg levels by at least 1g/L. FFP has previously been shown to improve coagulation abnormalities and to control bleeding in patients with ALL and disseminated intravascular coagulation.[15] In contrast, no previous experience of the use of Fg concentrates has been reported in this particular clinical situation.

Venous thrombosis is the most severe adverse event during induction therapy for ALL in patients receiving L-asparaginase, and such a complication occurred in 9.3% of patients in the CAPELAL cohort. The rate of thrombosis was lower in one large retrospective study (4.2%) involving 238 patients[17] and in one recent meta-analysis (5.9%) including 323 adults patients[18] but the use of relatively high doses of L-asparaginase in our patients might have in part contributed to these differences. The risk of thrombosis is presumably lower in children with ALL and was evaluated at 5.2% in a recent meta-analysis of 17 prospective studies comprising 1752 pediatric patients.[19] Environmental risk factors for thrombosis are more frequent in adults than in children, but the only such factor clearly identified in our series was the use of oral contraceptives in women before induction. We did not, therefore, find any correlation between a very low Fg level (below 0.5 g/L) and thrombosis as previously reported,[20] not did we confirm the increased incidence of thrombosis in ALL patients with a T-cell immunophenotype.[21] Central venous catheters and genetic polymorphisms such as factor V Leiden and factor II 20210A have been associated with thrombosis in children,[22,23] but we did not systematically look for these hereditary risk factors in our adult population. Acquired AT deficiency was frequently detected in patients with thrombosis (70%), but a similar defect was also present in patients without thrombosis. However, the rate of thrombosis was lower in patients who had received AT concentrates (4/88, 4.5%) than in those who had not (16/126, 12.7%, p=0.04). In addition, a significant increase in AT levels (from 60 to 88%, p<0.0001) was only achieved after infusion of Aclotine®. These findings therefore indicate that infusion of AT concentrates in patients with ALL treated with L-asparaginase may result in a significant clinical benefit in terms of preventing thrombosis.

The association between treatment with L-asparaginase, acquired AT deficiency and thrombosis has been found previously in several studies in which L-asparaginase was administered in induction or consolidation phase therapy.[13,22-26] Several studies have also evaluated the potential benefit of AT concentrates in children and adults with ALL. Most measured surrogate markers evaluating thrombin generation[27-30] and only one reported a lower incidence of thrombosis in patients treated with AT (0 events in 17 treated cases *vs.* 10 events in 37 patients not receiving AT, p=0.021).[21] Although none of our patients died from thrombosis, overall and disease-free survival rates were decreased among the patients who had experienced a thrombotic event. We cannot exclude the possibility that the withdrawal of L-asparaginase because of coagulation abnormalities or thrombosis might have influenced the outcome of some patients. The fact that preventive administration of AT was associated with a lower rate of delayed treatment with L-asparaginase or a reduced number of injections, supports this hypothesis. Asparaginase was not administered in the other phases of treatment and we did not find any significant delay in the consolidation and maintenance therapy of patients with thrombosis.

CAPELAL is a retrospective study and the absence of stringent guidelines for the management of hemostasis abnormalities is, therefore, a significant limitation. Nonetheless, this study strongly suggests that replacement therapy with AT concentrates has a beneficial effect by decreasing the rate of thrombosis and improving overall survival in adult patients with ALL treated with L-asparaginase. Prospective studies are essential to confirm these findings.

Authorship and Disclosures

MH, AM, NI and YG designed the research, PC, MD, CEB, SB, MB, IL, and JC included patients and revised the manuscript. MH and YG analyzed data and wrote the paper. AT, BP and NI revised the manuscript.

AT and BP are currently employees of LFB. MH, AM and YG have received consultation fees from the LFB. None of the other authors has any conflicts of interest to declare.

References

1. Clavell L, Gelber R, Cohen H, Hitchcock-Bryan S, Cassady J, Tarbell N, et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. N Engl J Med 1986;315:657-63.
2. Duval M, Suciu S, Ferster A, Rialland X, Nelken B, Lutz P, et al. Comparison of Escherichia coli-asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer-Children's Leukemia Group phase 3 trial. Blood 2002;99:2734-9.
3. Larson RA, Fretzin MH, Dodge RK, Schiffer CA. Hypersensitivity reactions to L-asparaginase do not impact on the remission duration of adults with acute lymphoblastic leukemia. Leukemia 1998;12:660-5.
4. Nagura E, Kimura K, Yamada K, Ota K, Maekawa T, Takaku F, et al. Nation-wide randomized comparative study of doxorubicin, vincristine and prednisolone combination therapy with and without L-asparaginase for adult acute lymphoblastic leukemia. Cancer Chemother Pharmacol 1994;33:359-65.
5. Mitchell LG, Halton JM, Vegh PA, Barr RD, Venneri T, Pai KM, et al. Effect of disease and chemotherapy on hemostasis in children with acute lymphoid leukemia. Am J Pediatr Hematol Oncol 1994;16:120-6.
6. Hunault M, Harousseau J, Delain M, Truchan-Graczyk M, Cahn J, Witz F, et al. Better outcome of adult acute lymphoblastic leukemia after early genoidentical allogeneic bone-marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: a GOELAMS trial. Blood 2004;104:3028-37.
7. Hunault M, Truchan-Graczyk M, Caillot D, Harousseau JL, Bologna S, Himberlin C, et al. Outcome of adult T-lymphoblastic lymphoma after acute lymphoblastic leukemia-type treatment: a GOELAMS trial. Haematologica 2007;92:1623-30.
8. Hoelzer D, Thiel E, Loffler H, Bodenstein H, Plaumann L, Buchner T, et al. Intensified therapy in acute lymphoblastic and acute undifferentiated leukemia in adults. Blood 1984; 64:38-47.
9. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86:1327-30.
10. Andrew M, Brooker L, Mitchell L. Acquired antithrombin III deficiency secondary to asparaginase therapy in childhood acute lymphoblastic leukaemia. Blood Coagul Fibrinolysis 1994;5 (Suppl 1):S24-36.
11. Legnani C, Palareti G, Pession A, Poggi M, Vecchi V, Bianchini B, et al. Intravascular coagulation phenomena associated with prevalent fall in fibrinogen and plasminogen during L-asparaginase treatment in leukemic children. Haemostasis 1988;18:179-86.
12. Miniero R, Pastore G, Saracco P, Messina M, Lange MM, Fiandino G, et al. Hemostatic changes in children with acute lymphoblastic leukemia treated according to two different L-asparaginase schedules. Am J Pediatr Hematol Oncol 1986;8:116-20.
13. Mitchell LG, Sutor AH, Andrew M. Hemostasis in childhood acute lymphoblastic leukemia: coagulopathy induced by disease and treatment. Semin Thromb Hemost 1995;21:390-401.
14. Leone G, Gugliotta L, Mazzucconi MG, De Stefano V, Belmonte MM, Dragoni F, et al. Evidence of a hypercoagulable state in patients with acute lymphoblastic leukemia treated with low dose of E. coli L-asparaginase: a GIMEMA study. Thromb Haemost 1993;69:12-5.
15. Sarris A, Cortes J, Kantarjian H, Pierce S, Smith T, Keating M, et al. Disseminated intravascular coagulation in adult acute lymphoblastic leukemia: frequent complications with fibrinogen levels less than 100 mg/dl. Leuk Lymphoma 1996;21:85-92.
16. Hongo T, Okada S, Ohzeki T, Ohta H, Nishimura S, Hamamoto K, et al. Low plasma levels of hemostatic proteins during the induction phase in children with acute lymphoblastic leukemia: a retrospective study by the JACLS. Japan Association of Childhood Leukemia Study. Pediatr Int 2002;44:293-9.
17. Gugliotta L, Mazzucconi MG, Leone G, Mattioli-Belmonte M, Defazio D, Annino L, et al. Incidence of thrombotic complications in adult patients with acute lymphoblastic leukaemia receiving L-asparaginase during induction therapy: a retrospective study. The GIMEMA Group. Eur J Haematol 1992;49:63-6.
18. Caruso V, Iacoviello L, Di Castelnuovo A, Storti S, Donati MB. Venous thrombotic complications in adults undergoing induction treatment for acute lymphoblastic leukemia: results from a meta-analysis. J Thromb Haemost 2007;5:621-3.
19. Caruso V, Iacoviello L, Di Castelnuovo A, Storti S, Mariani G, de Gaetano G, et al. Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. Blood 2006; 108:2216-22.
20. Beinart G, Damon L. Thrombosis associated with L-asparaginase therapy and low fibrinogen levels in adult acute lymphoblastic leukemia. Am J Hematol 2004;77:331-5.
21. Elliott M, Wolf R, Hook C, Pruthi R, Heit J, Letendre L, et al. Thromboembolism in adults with acute lymphoblastic leukemia during induction with L-asparaginase-containing multi-agent regimens: incidence, risk factors, and possible role of antithrombin. Leuk Lymphoma 2004;45: 1545-9.
22. Mauz-Korholz C, Junker R, Gobel U, Nowak-Gottl U. Prothrombotic risk factors in children with acute lymphoblastic leukemia treated with delayed E. coli asparaginase (COALL-92 and 97 protocols). Thromb Haemost 2000;83:840-3.
23. Nowak-Gottl U, Wermes C, Junker R, Koch HG, Schobess R, Fleischhack G, et al. Prospective evaluation of the thrombotic risk in children with acute lymphoblastic leukemia carrying the MTHFR TT 677 genotype, the prothrombin G20210A variant, and further prothrombotic risk factors. Blood 1999;93:1595-9.
24. Mitchell L, Andrew M, Hanna K, Abshire T, Halton J, Anderson R, et al. A prospective cohort study determining the prevalence of thrombotic events in children with acute lymphoblastic leukemia and a central venous line who are treated with L-asparaginase: results of the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) Study. Cancer 2003;97: 508-16.
25. Mitchell L, Hoogendoorn H, Giles AR, Vegh P, Andrew M. Increased endogenous thrombin generation in children with acute lymphoblastic leukemia: risk of thrombotic complications in L-asparaginase-induced antithrombin III deficiency. Blood 1994;83:386-91.
26. Sutor AH, Mall V, Thomas KB. Bleeding and thrombosis in children with acute lymphoblastic leukaemia, treated according to the ALL-BFM-90 protocol. Klin Padiatr 1999;211:201-4.
27. Gugliotta L, D'Angelo A, Mattioli Belmonte M, Vigano-D'Angelo S, Colombo G, Catani L, et al. Hypercoagulability during L-asparaginase treatment: the effect of antithrombin III supplementation in vivo. Br J Haematol 1990;74:465-70.
28. Mattioli Belmonte M, Gugliotta L, Delvos U, Catani L, Vianelli N, Cascione ML, et al. A regimen for antithrombin III substitution in patients with acute lymphoblastic leukemia under treatment with L-asparaginase. Haematologica 1991; 76:209-14.
29. Mazzucconi MG, Gugliotta L, Leone G, Dragoni F, Belmonte MM, De Stefano V, et al. Antithrombin III infusion suppresses the hypercoagulable state in adult acute lymphoblastic leukaemia patients treated with a low dose of Escherichia coli L-asparaginase. A GIMEMA study. Blood Coagul Fibrinolysis 1994;5:23-8.
30. Pogliani EM, Parma M, Baragetti I, Mostarda G, Rivolta F, Maffe P, et al. L-asparaginase in acute lymphoblastic leukemia treatment: the role of human antithrombin III concentrates in regulating the prothrombotic state induced by therapy. Acta Haematol 1995;93:5-8.