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Acute promyelocytic leukaemia and acquired α -2-plasmin inhibitor deficiency: a retrospective look at the use of epsilon-aminocaproic acid (Amicar) in 30 patients

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Abstract

Bleeding diathesis and a hyper-fibrinolytic state often accompany a diagnosis of Acute Promyelocytic Leukaemia (APML). This complication can have grave effects if not successfully treated, with a 10–20% incidence of haemorrhagic death. We hypothesized that α -2-antiplasmin levels would correlate with the risk for bleeding, and that administration of epsilon-aminocaproic acid (EACA) would attenuate that risk. To assess this, we conducted a retrospective chart review analyzing 30 APML patients, 17 of whom were treated with EACA. Thirty patients were treated, 21 with primary induction therapy. Patients with low α -2-antiplasmin levels were treated with a coagulopathy protocol consisting of low-dose heparin, EACA and blood product support. Seventeen patients (57%) developed haemorrhagic complications during their treatment. The presence and grade of haemorrhage appeared to be associated with the α -2-antiplasmin level. There were no grade IV haemorrhages or episodes of haemorrhagic death. One episode of central venous catheter associated thromboembolism and three deaths from infection during chemotherapy were observed. α -2-Antiplasmin levels are a reliable surrogate for fibrinolysis and haemorrhagic risk in patients with APML. Treatment with EACA is a rational way to pharmacologically inhibit fibrinolysis, is associated with a low incidence of severe haemorrhagic events, and appears to be safe with a low risk of thrombosis. Randomized clinical trials further assessing the efficacy and potential toxicity of EACA in inhibiting fibrinolysis in patients with APML are needed.

Keywords

acute promyelocytic leukaemia; fibrinolysis; anti-fibrinolytic agents

Introduction

Acute promyelocytic leukaemia (APML) is a distinct acute myelogenous leukaemia (AML) subtype characterized by its unique molecular (PML/RAR- α), cytogenetic (t15:17) and clinical (coagulopathy) features [1]. This relationship between APML and coagulopathy is well established with some reports showing that as many as 85% of patients develop

disseminated intravascular coagulation (DIC) at presentation or shortly after the initiation of induction chemotherapy [2].

The mechanism behind this bleeding diathesis is incompletely understood, but is felt to be due to the development of DIC, activation of the fibrinolytic system, or both. The membrane receptor Annexin II is thought to play a significant role in the coagulopathy. Annexin II markedly enhances plasmin generation by acting as a receptor for plasminogen and tissue plasminogen activator [3,4]. Excessive generation of plasmin causes depletion of its natural inhibitor, α -2-antiplasmin, leading to an uncontrolled fibrinolytic state and a bleeding diathesis [5]. This hyperfibrinolytic state can have grave effects, as up to 40% of patients develop a pulmonary or cerebro-vascular haemorrhage, with a 5–10% incidence of haemorrhagic death [6].

The introduction of the differentiating agent all-*trans* retinoic acid (ATRA) in the treatment of APML has markedly changed the course of the disease. Use of ATRA in combination with cytotoxic chemotherapy produces complete response (CR) rates of up to 95%, and by far the highest cure rate of any of the variants of acute myeloid leukaemia [7]. This therapy is relatively non-toxic and has shown substantial benefits in the elderly population, with a CR of above 80% in some studies [8]. While the use of ATRA has significantly reduced the incidence of the haemorrhagic complications associated with APML to 5–10%, the risk for haemorrhagic death remains significant (approximately 10%) [9].

A number of different treatment strategies have been proposed for APML-related coagulopathy, but the optimal strategy remains unclear. A previous report from our group described the use of combined epsilon-aminocaproic acid (EACA) and heparin in seven patients with APML-related bleeding [10]. We showed that the plasma α -2-plasmin inhibitor level is a useful indicator of both excessive fibrinolytic activity and bleeding risk in patients with APML, and used a low α -2-antiplasmin level as an indicator for treatment with EACA and heparin. Treatment with EACA and heparin successfully reversed clinical bleeding in these seven patients, with no episodes of severe or life-threatening haemorrhage. Concern that antifibrinolytic treatment would create a high risk of thrombosis was not borne out, with only one episode of thrombosis of a central venous catheter among the treated patients [10]. We now present our institutional experience of the use of heparin and EACA therapy in 30 patients with acute promyelocytic leukaemia and acquired α -2-plasmin inhibitor deficiency.

Methods

Study design

We retrospectively reviewed all of the cases of acute promyelocytic leukaemia that were diagnosed and treated at the University of Wisconsin Hospital and Clinics between January 1983 and February 2001. Thirty patients were diagnosed with and/or treated for APML during that time period and were eligible for evaluation.

Measurement of fibrinolytic activity

Fibrinolytic activity was assessed by the measuring depletion of alpha-2-antiplasmin, the physiologic inhibitor of plasmin. Peripheral blood was collected from the patients and sent to the UW Core Laboratory where the α -2-antiplasmin activity level was ascertained. From 1983 until December 1992 the antiplasmin activity was determined using a fluorogenic assay (Dade Protopath, normal range 79–118% of the activity in pooled normal plasma). In December 1992 this assay was replaced by a chromogenic method (Chromogenix Coamatic Plasmin Inhibitor, normal range 85–150% of the activity in pooled normal plasma), which was used throughout the remainder of the study period. α -2-Antiplasmin levels were

determined by both methods for seven of the patients treated during the study, and the chromogenic assay consistently showed higher levels of α -2-antiplasmin activity by approximately 10–15%.

Acute promyelocytic leukaemia management strategy

Patients with APML were considered to have a coagulopathy with the following: INR >1.6, fibrinogen <75, α -2-antiplasmin level <50% and/or physical signs of bleeding. The following comprehensive strategy for the management of this coagulopathy in APML patients was used: (1) unfractionated heparin loading dose of 2500 U/h followed by a continuous infusion of 500 U/h; (2) vitamin K 10mg subcutaneous twice weekly; (3) if INR >1.6, give fresh frozen plasma (FFP) every 8 h; (4) if fibrinogen <75 mg/dl (dl, decilitre), give cryoprecipitate 1 bag/10 kg/ every 8 h; (5) if α -2-antiplasmin level <50%, begin EACA 6 g intravenous loading dose followed by 1 g/h continuous infusion. The EACA infusion was continued until the α -2-antiplasmin level was >50% for two consecutive days. The heparin infusion was continued until the coagulopathy was resolved, which was defined as the following:

1. INR <1.6 without FFP;
2. fibrinogen >150 without FFP or cryoprecipitate;
3. α -2-antiplasmin >75% without FFP or EACA.

Haemorrhagic event classification

Haemorrhagic events were classified according to Common Toxicity Criteria as follows: grade 0 (no haemorrhage), grade I (minor bleeding), grade II (moderate bleeding not requiring a transfusion), grade III (bleeding requiring transfusion), grade IV (catastrophic bleeding requiring major non-elective intervention), and grade V (death).

Statistical analysis

Categorical data were summarized as frequencies and percentages. All quantitative data were summarized by medians or means. Correlation coefficients were calculated using a single factor ANOVA analysis.

Results

Patient characteristics

Thirty patients with acute promyelocytic leukaemia were treated at the University of Wisconsin between January 1983 and February 2001. Of the 30 patients, 21 were given induction chemotherapy for the newly diagnosed disease, while nine received re-induction therapy for relapsed disease. All of the patients receiving initial induction therapy were treated with an anthracycline containing a chemotherapy regimen, with a CR of 76% (16/21), while those receiving re-induction after relapse were treated with a variety of protocols (ex. etoposide/daunorubicin, carboplatin). Many of these patients were treated in the pre-all-*trans*-retinoic-acid era, and as a result ATRA was only included in 11/30 (37%) of the treatment courses. Seventeen of the 30 patients (56.6%) were treated with EACA according to our APML protocol as stated above, while 13 patients did not require EACA therapy. The characteristics of the patients at the time of beginning induction or re-induction therapy are given in Table 1.

Haemorrhagic events and α -2-antiplasmin levels

Seventeen out of the 30 patients (57%) developed haemorrhagic complications during the course of their treatment. These consisted of five grade I (29%), three grade II (18%) and

nine grade III (53%) haemorrhagic events. There were no grade IV or grade V haemorrhagic events. We assessed the development of a bleeding diathesis in APML patients as a function of their α -2-antiplasmin level and found the following: 53% of the haemorrhagic events occurred in patients with an α -2-antiplasmin level <25%, 6% in patients with a level of 26–50%, 29% in patients with a level of 51–75% and 12% in patients with a level of >76% (Figure 1).

The finding of a low α -2-antiplasmin level was correlated with a higher incidence of overall bleeding ($F=54.39$, $p=0.002$). In addition, haemorrhagic events by grade were evaluated by severity with grade III bleeding showing a significant association with α -2-antiplasmin levels as follows: 67% of the grade III haemorrhages occurred in patients with α -2-antiplasmin levels of <25%, 22% of grade III haemorrhages occurred in patients with α -2-antiplasmin levels of 51–75% and 11% occurred in patients with levels >76% ($F=58.07$, $p=0.002$). In contrast, the percentage of grade I and II haemorrhagic events did not correlate with the α -2-antiplasmin activity level. Thirty-three percent of the grade II events occurred in <25%, 51–75% and >76% α -2-antiplasmin activity levels respectively. Grade I haemorrhagic events were distributed across α -2-antiplasmin activity levels as 40%, 20% and 40% in <25%, 26–50% and 51–75% levels respectively. The haemorrhagic events by α -2-antiplasmin activity levels are summarized in Figure 1.

Management of APML associated coagulopathy

Utilizing the UW comprehensive coagulopathy management strategy, 100% of the patients in this series received vitamin K, a low-dose heparin infusion, blood and platelet transfusions (mean 14.4 units and 58.5 units respectively). In addition, 53% and 40% patients received fresh frozen plasma and cryoprecipitate (mean 11.9 units and 38.9 units respectively).

Response and adverse events with therapy

Twenty-one of the 30 patients were treated with induction chemotherapy for APML and 15/21 (71%) of those patients achieved a complete remission. Three patients (10%) undergoing induction therapy died of infectious complications. There were no haemorrhagic deaths and only one clinically apparent catheter-associated episode of venous thromboembolism in this series. Of note, there was no effort to identify asymptomatic episodes of venous thromboembolism in this series.

Discussion

While the pathogenesis of the coagulopathy associated with APML is under some debate, both the procoagulant and fibrinolytic properties of leukaemic cells have been well studied [11–13]. The procoagulant activities of leukaemic cells appear to be related to the increased expression of tissue factor (TF) or cancer procoagulant (CP). As is well known, TF forms a complex with factor VII to activate factors X and IX to activate and accelerate the coagulation process. CP, a cysteine proteinase found in leukaemic cells, has been shown to directly activate factor X independently of the presence of factor VII to initiate the coagulation cascade [12]. However, the exact mechanism of action of cancer procoagulant and its overall level of importance is still unknown with *in vitro* studies showing that cancer procoagulant's effect on blood coagulation is several magnitudes lower than that of TF [13].

The role of heparin in the treatment of this procoagulant state in APML continues to be a matter of debate. Theoretically, heparin would have benefit as it inactivates factor X through an anti-thrombin dependent pathway and promotes the release of the tissue factor pathway inhibitor [14]. Majority of the research on the use of heparin in APML was performed in the

1970s–1980s and they gave conflicting results, with the majority of studies showing no benefit in terms of CR rates and some even suggesting an increased risk of haemorrhagic events and mortality in the heparin treated patients [15]. However, these studies must be interpreted with caution as many of them had substantial limitations including small sample size, lack of a control arm and were largely retrospective analyses. The use of low dose unfractionated heparin in our protocol is intended to prevent the theoretical pro-thrombotic effect of concomitant EACA therapy as well as the procoagulant component of DIC. We believe this is a safe and efficacious strategy, as there were no severe thrombotic or haemorrhagic events observed in any of our patients.

The profibrinolytic properties of leukaemic cells have also been well studied and described. Leukaemic promyelocytes have been shown to contain tissue plasminogen activator (t-PA) as well as the proteases elastase and chymotrypsin [12]. These enzymes can degrade a number of clotting factors as well as α -2-antiplasmin and C1 esterase inhibitor, the two natural inhibitors of plasmin [16]. More recently, it has been discovered that increased expression of Annexin II in APML leukaemic cells leads to an increase in the production of plasmin by these cells [3]. A number of other risk factors for bleeding and haemorrhagic death in APML have been identified in previous studies including: age >50, blast count >1000/mm³, haemoglobin <10 g/dl, and the inability to maintain a platelet count >4000/mm³ [17,18]. Our data suggest that acquired deficiency of α -2-antiplasmin, the natural inhibitor of plasmin, should also be considered an indicator of bleeding risk in patients with APML. We observed a significant increase in the number and severity of haemorrhagic events as the level of α -2-antiplasmin activity decreased as determined in the *p*-values from the single factor ANOVA analysis of both the overall number of haemorrhages and for the increasing number of grade three haemorrhages. These findings are consistent with previous studies that have shown that α -2-antiplasmin deficiency is correlated with systemic fibrinolysis, particularly in patients with acute promyelocytic leukaemia [5,19].

Given the central role of plasmin/plasminogen and associated inhibitors in the fibrinolytic state associated with APML as described above, the use of epsilon-aminocaproic acid for the treatment of this bleeding diathesis makes intuitive sense as it has been found to be an effective *in vitro* inhibitor of plasminogen activation and fibrinolysis [20]. Indeed, recent placebo controlled studies have shown EACA to be effective in decreasing the *in vivo* bleeding diathesis and blood product consumption associated with a number of surgical procedures including hip and knee replacements as well as coronary artery bypass grafting; as well as medical conditions such as cirrhosis [21–23].

The comprehensive strategy for the management of the coagulopathy associated with APML described here, consisting of low dose heparin and EACA therapy in addition to blood product support, was apparently effective in preventing haemorrhagic complications during APML treatment. While 57% of our patients had haemorrhagic events, there were no grade IV haemorrhages or deaths from bleeding. This is particularly significant as many of these subjects were treated in the era prior to the use of ATRA therapy. In contrast, other studies of patients treated solely with blood product support describe approximately a 20% incidence of severe (grade IV) haemorrhages and a 10–15% mortality rate from bleeding [24]. Even in the post-ATRA treatment era, studies have shown high rates of fatal haemorrhage (20–50%) from the coagulopathy associated with APML [17,25].

There have been a few studies that suggested an increased risk of thromboembolism in patients receiving EACA [26–28]. The largest series of patients was published by Brown *et al.* [26] in 2000, who reported their experience treating 31 patients with APML. They observed seven deaths in this series of patients, with four of these considered early deaths (<42 days) that only occurred in the subjects who received ATRA and anti-fibrinolytic

therapy. At autopsy, three out of the four early deaths were felt to be secondary to widespread micro-vascular thrombosis. We did not observe this phenomenon of diffuse thrombosis with the use of anti-fibrinolytic therapy. This may have been due to the inclusion of continuous low-dose unfractionated heparin in combination with EACA. Four of the 11 patients in our series who received ATRA were given combination heparin and EACA therapy, with no serious thrombotic events observed.

A second concern is whether or not EACA would be effective in preventing fatal haemorrhagic events given the recently published negative results seen with the use of tranexamic acid in this setting by the PETHEMA study group [29]. Regarding this, we feel that there are a number of important differences in that study as compared to our study. First, in the PETHEMA study all patients with a platelet count $<50,000/l$ and clinical signs of a coagulopathy (not otherwise specified) were treated with tranexamic acid until either one of those factors had been reversed. In our study, aminocaproic acid was given only when the α -2-antiplasmin level was $<50\%$. It may well be that following α -2-antiplasmin levels is a more specific marker for anti-fibrinolytic therapy. It may be that depressed levels of α -2-antiplasmin levels allowed us to start anti-fibrinolytic therapy sooner and avoid the early mortality seen from haemorrhagic events in the PETHEMA study. Second, the study by De la Serna *et al.* did not use heparin therapy unless there was a thrombotic event. In our study, all patients were treated with heparin until the resolution of their coagulopathy (defined as INR <1.6 without FFP, fibrinogen >150 without FFP or cryoprecipitate and α -2-antiplasmin $>75\%$ without FFP or aminocaproic acid. It is possible that the uniform use of heparin therapy in our study patients prevented the increase in adverse thrombotic events seen in the PETHEMA study with the use of tranexamic acid. Third, there may be inherent pharmacologic differences between tranexamic acid and aminocaproic acid. It is possible that the dose of tranexamic acid given in the PETHEMA study was not biologically equivalent to the dose of EACA given in our study. Further study on the dosing and measurement of effect is warranted for each of these anti-fibrinolytic agents.

While there is evidence in this series that α -2-antiplasmin levels are a reliable surrogate for the coagulopathy associated with APML and that the use of heparin and EACA may decrease the morbidity and mortality associated with bleeding, there are limitations to the study and these findings. This study is a retrospective review and not a controlled clinical trial, so it is not possible to prove a causal effect of EACA on the prevention of haemorrhagic events. Second, as this study was not randomized there is the possibility that the observed associations are due to any number of factors such as chance, patient selection or referral bias to name a few. Third, the relatively small sample size also makes drawing any definitive conclusions difficult. The above listed limitations point to the need for a randomized controlled trial to further elucidate the findings of this study. This type of study would be difficult for a single institution given the relative rarity of the diagnosis of APML compared to other types of leukaemia, but should be considered in a cooperative group setting.

Despite these limitations, we feel that this retrospective study shows that α -2-antiplasmin levels are a useful indicator of fibrinolysis and haemorrhagic risk in patients with acute promyelocytic leukaemia. Our data also suggest that the coagulopathy in APML can successfully be managed with a comprehensive strategy including low-dose heparin infusion, EACA infusion and blood product support, with a low risk for haemorrhage-related morbidity and mortality. The combination of low-dose heparin and epsilon-aminocaproic acid appears to be safe in patients with acute promyelocytic leukaemia, with a low risk for thrombosis.

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Figure 1.
Number and grade of haemorrhagic events by α -2-antiplasmin level

Table 1

Participating patient characteristics

	Patients n=30
Median age (years)	49
Gender	
Male	18 (60%)
Female	12 (40%)
Blood counts	
Blast count >1000/mm ³	9 (30%)
Hemoglobin <10 g/dl	14 (47%)
Platelets <30,000/mm ³	13 (43%)
Type of therapy	
Primary induction	21 (70%)
Re-induction	9 (30%)
ATRA	11(37%)
Coagulopathy strategy	
Vitamin K	30 (100%)
Heparin	30 (100%)
Blood transfusion (mean units)	11.4
Platelet transfusion (mean units)	58.5
Fresh frozen plasma (mean units)	11.9
Cryoprecipitate (mean units)	38.9