Clinical Medicine

Acute Promyelocytic Leukemia

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Acute promyelocytic leukemia (APL) is a subtype of acute myelogenous leukemia frequently associated with disseminated intravascular coagulation (DIC). Data on 11 patients with APL treated at our institution were analyzed and compared with those of 147 published cases. Most had a bleeding diathesis at presentation and evidence of DIC eventually developed in all. Seven patients (64%) showed the t(15;17)(q22;q21) karyotype or a similar translocation. Using a chemotherapy induction regimen containing an anthracycline, complete remission, requiring a total of 14 courses of treatment, was achieved in six patients (55%). The median duration of response and median survival for complete responders were 10 and 15 months, respectively. Three patients (27%) died of bleeding complications during induction therapy. The tritiated-thymidine labeling index of leukemia cells predicted which patients would achieve a complete remission. Review of six studies of 147 patients with APL from the past 12 years supports the use of a chemotherapy induction regimen containing anthracycline or amsacrine and heparin for the treatment of DIC.

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Acute promyelocytic leukemia (APL) is a subtype of acute myelogenous leukemia (AML) characterized by proliferating abnormal promyelocytes. Most patients with this disorder present with a hemorrhagic diathesis usually associated with disseminated intravascular coagulation (DIC). It is often difficult to successfully induce remission because of DIC-associated hemorrhagic complications, particularly cerebral hemorrhage. Baker and co-workers were the first to report more than 20 years ago the successful use of heparin in the treatment of DIC in a patient with APL.[1] Eight years later Gralnick and associates confirmed the beneficial effects of using heparin in three patients with APL.[2] Since that time no prospective randomized study has been carried out, and recently some investigators have questioned the efficacy of using heparin in treating this disorder.[3] There is, therefore, still some controversy regarding the ideal supportive measures necessary for inducing remission in APL.

Another characteristic of APL, reported by some investigators, is a survival advantage for complete responders when compared with other subtypes of acute myelogenous leukemia.[4-6] This possible survival advantage theoretically would offset the increased number of early deaths associated with DIC-related hemorrhagic complications occurring during induction chemotherapy, resulting in long-term survival rates comparable to those seen with other subtypes of acute myelogenous leukemia.

A third purported characteristic of APL is an apparent resistance to standard chemotherapy in some patients.[7] Bernard and colleagues first showed a definite therapeutic efficacy with the use of daunorubicin hydrochloride in this disorder.[6] This was later confirmed by others.[4,8] Several authors, however, noted that many patients require several courses of chemotherapy to induce remission.[6,7] But investigators more recently have emphasized that complete remission in patients with APL can occur without marrow aplasia and that a pattern of leukemic cell differentiation may occur.[4,9,10] This is obviously a very important point in initially monitoring patients.

In this review we evaluate our experience with APL and contrast and compare our findings with those published in the literature with respect to the three specific issues introduced above. We also make detailed recommendations regarding the treatment of the DIC associated with APL. The possible role of a pretreatment tritiated-thymidine labeling index of leukemic cells as a prognostic factor in this disorder is discussed.

Methods

Eleven previously untreated patients with APL who received induction chemotherapy within the past seven years at the University Medical Center of the University of Arizona College of Medicine, Tucson, are described. The diagnosis of APL was made on the basis of pretreatment blood smears, bone marrow aspiration and biopsy and cytogenetic findings. Our criteria for APL are those of the French-American-British cooperative group.[11] The one-stage prothrombin time (PT) was determined using dried rabbit brain thromboplastin with calcium (Thromboplastin C, Dade Diagnostics, Inc, Aguada, Puerto Rico), and an activated partial thromboplastin time (PTT) was measured using liquid rabbit brain cephalin with plasma activator (Actin, Activated Cephaloplastin Reagent, Dade Diagnostics, Inc). Fibrinogen levels measured using Data-fi Thrombin Reagent (Dade Diagnostics, Inc) and fibrin- and fibrinogen-degradation products were measured using the Thrombo-Wellcotest (Wellcome Diagnostics, Dartford, England). The above coagulation tests

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ABBREVIATIONS USED IN TEXT

AAT = amsacrine, ara-C (cytarabine) and thioguanine
AML = acute myelogenous leukemia
APL = acute promyelocytic leukemia
DAT = daunorubicin hydrochloride, ara-C (cytarabine) and thioguanine
DIC = disseminated intravascular coagulation
PT = prothrombin time
PTT = partial thromboplastin time

were done at the time of diagnosis and generally two to three times a day while patients were receiving heparin. The tritiated-thymidine labeling index was determined as previously described,[12] using bone marrow cells obtained before initiating induction chemotherapy. Leukemic promyelocytes plus blasts were counted for labeling.

All patients were treated with anthracycline or cytarabine institutional chemotherapeutic protocols for acute nonlymphocytic leukemia (see Table 1). DIC was defined as the presence of fibrinogen-split products at a level of 40 mg per dl or more with a low fibrinogen level (normal 150 to 400 mg per dl). Specific factor assays were not routinely done. All patients (except patient 2) were given heparin, which therapy was begun immediately before initiating chemotherapy. A loading dose of 5,000 units was administered as a bolus followed by a continuous infusion, initially at 7 to 10 units per kg body weight per hour. The heparin infusion was adjusted to maintain a fibrinogen level greater than 100 mg per dl. Patients continued to receive heparin until the coagulopathy resolved, which occurred as the leukemia went into remission. If fibrinogen levels were not corrected by heparin therapy alone without excessive prolongation of the partial thromboplastin time or were low to begin with, then cryoprecipitate was administered. Platelet transfusions were administered to maintain platelet counts above 30,000 per μl.

All patients were treated under conditions of reverse isolation. Laminar flow rooms were not routinely used. Fever and infection were treated aggressively in the usual manner by administering broad-spectrum antibiotics (generally, an aminoglycoside plus cephalosporin), with antifungal agents being added as needed. Two patients received granulocyte transfusions.

The criteria for complete remission were fewer than 5% myeloblasts in bone marrow specimens with morphologically normal-appearing promyelocytes and normal recovery of all elements. Coagulation test findings had to be normal. The duration of survival was calculated from the date of diagnosis (usually within a few days of the start of treatment).

Results

UMC Experience

A total of 11 patients with APL received treatment at the University Medical Center within the past seven years (Table 1). Four patients (36%) were male and the median age at diagnosis was 28 years. Most patients presented with a bleeding diathesis and all but one had laboratory evidence of DIC. DIC developed in that patient, however, when induction chemotherapy was begun. The median leukocyte count was 3,800 per μl with 73% (eight) of the patients having leukocyte counts less than 20,000 per μl. The median peripheral myeloblast count was 2%, promyelocytes 22% and neutrophils 7%. The median hemoglobin was 10.1 grams per dl. The median platelet count was 21,000 per μl, with 82% of the patients having counts less than 50,000 per μl. Five of eight patients in whom adequate karyotype determinations could be done showed the typical t(15;17)(q22;q21), or a similar translocation, before treatment. Six patients (55%) had complete remission; patient 5 required a single course of induction chemotherapy; patients 7, 8 and 9 received two courses; patient 10 received three courses, and patient 11 received four courses. Median survival was six months for all patients. The median duration of response and median survival for complete responders were 10 months and 15 months, respectively. Figure 1 shows the actuarial survival of all 11 patients. Three patients (27%) are alive and free of disease at 14, 31 and 80 months. If the single patient not treated with heparin (patient 2) is excluded from analysis, then 60% of our patients achieved a complete response, with a median survival of eight months.

Patients 1, 4 and 7 (27%) died of hemorrhage. All three hemorrhagic deaths (two from cerebral hemorrhage and one from gastrointestinal tract and pulmonary hemorrhage) oc-

TABLE 1.—*Patient Characteristics and Treatment Response at the University Medical Center, Tucson*

Patients	Age, Yr	Karyotype	Number of Induction Courses*	Response	Survival, Mo	Cause of Death
1	22	t(15;17)(q22;q21)†	1	Died	0.5	Subdural hematoma associated with DIC; persistent APL
2	2	t(15;17)(q22;q21)	1	Died	0.5	Sepsis, persistent APL
3	30	t(15;17)(q22;q21)†	1	CR	17	Sepsis, relapse APL
4	39	Normal	1	Died	0.5	GI tract and pulmonary hemorrhage associated with DIC; persistent APL
5	46	t(15;17)(q22;q21)	1	CR	13	Uncertain; APL relapse
6	51	t(15;17)(q22;q21)	1	Died	0.3	Sepsis, persistent APL
7	28	t(15;17)(q22;q21)	2	Died	0.1	Subdural hematoma associated with DIC; persistent APL
8	35	Normal	2	CR	72+	-----
9	22	Not determined	2	CR	27+	-----
10	23	Not determined	3	CR	10+	-----
11	18	t(15;17)(q22;q21)	4*	CR	13	Sepsis, relapse APL

APL = acute promyelocytic leukemia, CR = complete remission, DIC = disseminated intravascular coagulation, GI = gastrointestinal

*2 courses of a combination of anthracycline and cytarabine, plus 2 courses of a combination of BCNU (carmustine), cyclophosphamide (Cytoxan), vincristine sulfate, prednisone, methotrexate and methyl-glyoxal *bis*-guanylhydrazone (MGBG).

†In two patients, the karyotype was not found before treatment was started, but following relapse.

curred within 18 days of beginning induction chemotherapy. Patients 2, 3, 6 and 11 (36%) died of infection. Patient 11 died of infection during a relapse seven months after achieving a complete remission. Although the cause of death of patient 5 was unknown, there was no evidence of hemorrhage at the time of death. Persistent leukemia was present at the time of death in all eight patients. On evaluating the three patients who died of bleeding complications (1, 4 and 7), we found that two had active DIC at the time of death. The third patient had prolonged prothrombin and partial thromboplastin times but a normal fibrinogen level and no fibrin- or fibrinogen-split products. All three patients were receiving heparin, cryoprecipitate and platelet transfusions.

Most of our patients required escalation of the heparin dose to approximately 15 units per kg per hour and administration of large daily doses of cryoprecipitate (occasionally as many as three doses per day) to maintain fibrinogen levels of greater than 100 mg per dl. This was particularly the case during the first week of induction chemotherapy when DIC was the most severe.

Labeling index data were evaluated for two response categories designated A and B (Figure 2). Group A patients are those who achieved a complete remission, while group B patients are those who died within one month of the test without achieving a complete remission. Patients 3 and 5 achieved a complete remission initially, but later relapsed and died. Thus, they are included in both groups. Overall, the labeling index was lower in patients achieving a complete remission than in those who did not (Figure 2; $P = .06$). In group A, patient 5 required one course; patients 3, 8 and 9 required two courses of chemotherapy, and patient 10 three courses to achieve complete remission. In group B, patients 1 and 6 died of subdural hematoma and sepsis, respectively, with resistant APL within three weeks of receiving one course of chemotherapy. Patients 3, 5 and 11 all died in relapse after several chemotherapeutic regimens failed. Both patients 3 and 5 had higher labeling index values at relapse than earlier in their course.

Analysis of Previously Published Cases

Review of the literature showed that at least six studies of seven or more adult patients with APL have been published within the past 11 years (Table 2). A total of 147 patients from these studies was treated for their disease and their cases are, therefore, analyzed here. Two additional recent studies, presented only in abstract form, were excluded from this detailed analysis because much of the information required was not available.[9,10] Cases were stratified by type of induction chemotherapy given (± anthracycline) and by type of treatment for DIC (± heparin).

Only three of the six studies contain detailed data on DIC therapy. Collins and co-workers administered continuous infusions of heparin at 10 units per kg per hour without a loading dose. The heparin dose was adjusted to maintain the thrombin time between 20 and 60 seconds. Patients received heparin until the coagulopathy "demonstrated slowing." Cryoprecipitate was transfused to maintain the fibrinogen level at greater than 250 mg per dl. Fresh frozen plasma was given to maintain a factor V level at greater than 50%. Vitamin K and platelets were also administered. Drapkin and associates[14] and Arlin and colleagues[15] administered a continuous heparin infusion at 5 to 10 units per kg per hour for 5 to 14 days. The heparin dose was increased until "therapeutic levels were established," usually at 10 to 20 units per kg per hour. Coagulation factors were replaced with fresh frozen plasma and platelets were administered once or twice a day. Sufficient data concerning heparin treatment were available for a total of 60 patients. In all, 32 received heparin, of which 24 (75%) achieved a complete remission. Median survival for these patients was 15.0 months. Four (13%) died of DIC-related complications. Of the 28 who were not treated with heparin, 10 (36%) achieved a complete remission. Median survival for these patients was 0.8 months, which is signifi-

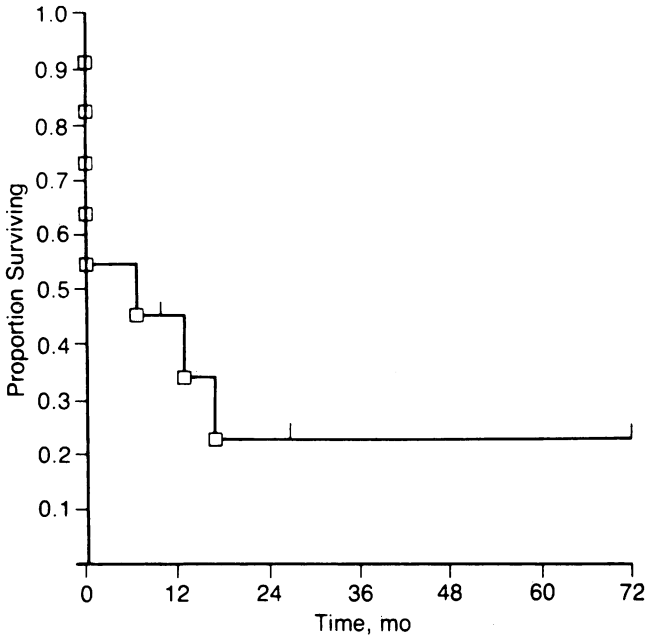

Figure 1.—Actuarial survival of all 11 patients treated at the University Medical Center of the University of Arizona College of Medicine, Tucson.

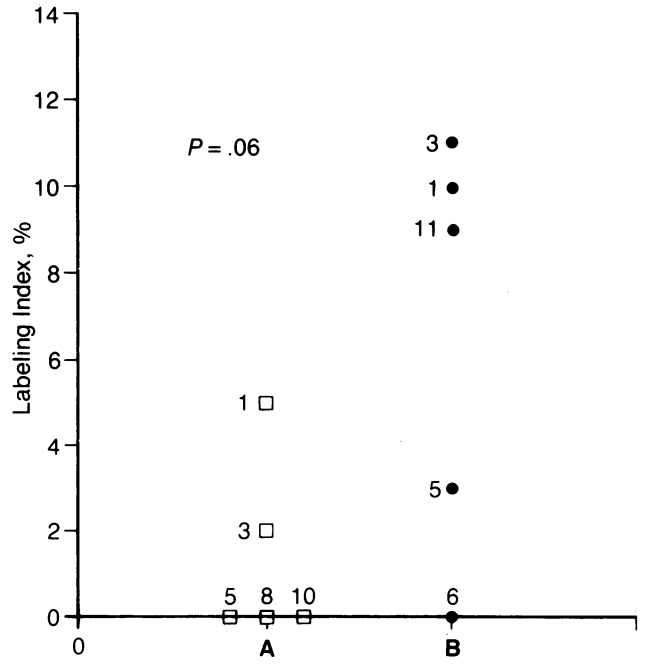

Figure 2.—Tritiated-thymidine labeling index of marrow blasts in acute promyelocytic leukemia. Group A patients (□) all had a complete remission. Group B patients (●) died of hemorrhagic complications with persistent acute promyelocytic leukemia. The patient number appears next to the labeling index value.

cantly less ($P = .019$) than the median survival of patients treated with heparin. There were 13 deaths related to DIC complications, which accounted for a total of 47% of the entire group, a figure significantly greater than that for patients treated with heparin ($P = .004$).

The median age of all 147 patients was 35 years and 51% were male. The median leukocyte count was 5,500 per μl, the median hemoglobin was 8.9 grams per dl and the median platelet count was 20,000 per μl. Of 84 evaluable patients, 73% (61) had DIC as defined by each institution's criteria.

The data in Table 2 are summarized in Table 3. Of the 147 evaluable patients, 69 (47%) had a complete remission and 52 patients (35%) died of DIC-related complications. The median survival for all patients was 2.2 months. Of the 147 patients, 107 were treated with anthracycline-containing combinations. Of the 107 patients, 61 (57%) achieved a complete remission, with a median survival for all 61 patients of 4.8 months. Of the 107 patients, 22 (21%) died of DIC-related causes. Of the 40 patients treated with combinations without anthracycline, 13 (33%) achieved a complete remission. The median survival for these patients was 0.5 months. This figure is significantly lower ($P = .035$) than the 4.8 months' survival in patients treated with anthracyclines. In the group not receiving anthracycline, 31 (78%) patients died of DIC-related complications, which is significantly greater than the 21% of patients treated with an anthracycline ($P = .001$). It should be noted that most of those patients achieving a complete remission were from Arlin's study and were treated with amsacrine.

Of all 147 patients, 32 were treated with either an anthracycline- or amsacrine-containing regimen plus heparin, and 22 (69%) achieved a complete remission. The median survival for all 32 patients was 15.0 months. Four patients (13%) died of DIC-related complications.

Discussion

Comparing the courses of the patients with APL treated at the University Medical Center within the past seven years with those of patients reported in the literature shows many similarities. Our patients were, however, younger, with a median age (28 years) that was about 20 years less than that reported for other patients with this subtype of AML. Most presented with hemorrhage associated with DIC. The peripheral leukocyte count was almost always below 20,000 per μl, a previously noted characteristic of APL not often seen in patients with other AML subtypes. The median platelet count was also lower than that usually seen with other subtypes of AML, probably a result of both marrow involvement with leukemia and of platelet consumption due to DIC. Most of our patients showed the typical t(15;17)(q22;q21), or a similar translocation, characteristic for this disease.[7,16-18] Overall, 55% (six) of our patients had a complete remission with a median duration of response of ten months. The median survival was six months. Excluding the 2-year-old patient not

TABLE 2.—*Summary of Published Cases and University Medical Center, Tucson, Series*

Patients, Number	Median Age, Yr	Sex Male, %	Patients With DIC, %	Karyotype t(15;17), %	Induction Chemotherapy	DIC Treatment	Patients Achieving CR, Number (%)	Median Duration of Responses, Mo	Deaths Due to DIC, Number (%)	Median Survival, Mo	References
30	..	..	..	...	Multiple regimens	Heparin (N=9), platelets	4 (13)	2	23 (77)	..	Bernard et al, 1973[6]
33	..	..	..	...	Daunorubicin hydrochloride		19 (55)	26	"Negligible"	..	
13	35	54	64	...	Daunorubicin or doxorubicin (Adriamycin) hydrochloride	Platelets	7 (54)	4.9	4 (31)	1	Ruggero et al, 1977[13]
7	39	71	71	...	Prednisone	Cryo, heparin, platelets, FFP	5 (71)	27	1 (14)	26	Collins et al, 1978[8]
7					Thioguanine+Ara-C	None	1 (14)	72	4 (57)	1	
8	39	54	79	...	Daunorubicin+Ara-C	None	2 (25)	35	5 (56)	1	Drapkin et al, 1978[14]
9					Daunorubicin+Ara-C	Heparin	7 (78)	15	2 (22)	10	
16	31	..	75	91	AMSA or thioguanine+Ara-C+daunorubicin	Heparin, platelets, FFP	12 (75)	10	1 (5)	..	Arlin et al, 1984[15]
21	28	56	72	100	Thioguanine+Ara-C+daunorubicin or thioguanine+Ara-C	Heparin (N=16)	11 (52)	17	9 (43)	5	Larson et al, 1984[7]
3							1 (33)	8	3 (100)	1	
11	28	36	100	63	[See Table 1]	Cryo, heparin, platelets	6 (55)	15	3 (27)	6	Current series
Totals 158	35	55	76	90			(47)		(44)	2.2	

AMSA=amsacrine, Ara-C=cytarabine, CR=complete remission, Cryo=cryoprecipitate, DIC=disseminated intravascular coagulation, FFP=fresh frozen plasma

TABLE 3.—*Summary of Table 2 by Treatment Type*

Patients, Number	Patient Treatment Category	Complete Remission, Number (Percent)	Median Survival, Mo	P Value (for MS)	DIC Deaths, Number (Percent)	P Value (for DIC Deaths)
147	All patients	69 (47)	2.2	....	52 (35)	....
40	Without anthracycline	13 (33)†	0.5	.035	31 (78)	.001
107	With anthracycline	61 (57)	4.8		22 (21)	
28*	Without heparin	10 (36)	0.8	.019	13 (47)	.004
32	With heparin	24 (75)	15.0		4 (13)	
32	With anthracycline or amsacrine, plus heparin	22 (69)	15.0	....	4 (13)	....

DIC=disseminated intravascular coagulation, MS=median survival

*Numbers add up to less than 147 because information on therapy for disseminated intravascular coagulation is incomplete.
†Most patients were treated with an amsacrine regimen.

treated with a regimen of heparin, 60% of our patients had a complete remission, with a median survival of eight months. The median survival of our patients does not differ significantly from that of cases reported in the literature in which the patients were treated with anthracycline- or amsacrine-containing regimens and heparin.

Three of our patients (27%) died of DIC-associated hemorrhage, which is higher than, but not significantly different from, the 13% of patients treated with heparin reported in the literature. The initial fibrinogen level has been noted by several investigators[6,8,13] to have prognostic significance. Five of our six patients who achieved complete remission had initial fibrinogen levels of greater than 100 mg per dl, whereas only two of the five patients who died during induction chemotherapy had fibrinogen levels greater than 100 mg per dl (data not shown; $P = .31$).

The labeling index served as a prognostic factor for our patients. With two exceptions, patients with a labeling index of 5% or less successfully achieved a complete remission. Of interest is that three of five patients with a labeling index of 5% or less still required two or more courses of chemotherapy to achieve a complete remission. Because in only one of our patients did a complete remission occur with only a single course of chemotherapy, evaluating the role of the labeling index for discriminating drug sensitivity was not possible.

One striking feature of our patient population was the apparent tumor resistance to standard chemotherapy. Only one of six patients achieving a complete remission did so with a single course of induction chemotherapy. Patients 7, 8 and 9 each required two courses of chemotherapy, patient 10 required three courses and patient 11 four courses of chemotherapy. This type of apparent drug resistance in cases of APL was also noted by Larson and co-workers.[7] Of their 13 patients, 8 showed evidence of significant drug resistance following the first course of chemotherapy and only 2 of these patients eventually had a complete remission with additional treatment. Of their entire group of 24 treated patients, 3 achieved a complete remission with one course of chemotherapy, 6 required two courses and 2 had a complete remission only after three or more courses of chemotherapy. This seeming drug resistance, however, may not be as substantial as first thought. In contrast to other subtypes of acute myelogenous leukemia, in APL *marrow aplasia may not be essential to accomplish remission.*[9,10] If significant—although perhaps not complete—cytoreduction occurs with one induction course, it may be wise to defer a second course until it is clear if remission will occur or, conversely, leukemia regrowth will ensue.

Despite the possibility of inherent drug resistance in cases of APL, it would appear that the highest rates of complete remission are achieved with the use of either amsacrine- or anthracycline-based regimens. This conclusion is supported by data recently published by Cunningham and associates in which 53 evaluable patients were treated with either daunorubicin hydrochloride, ara-C (cytarabine) and thioguanine (DAT) or AMSA (amsacrine), ara-C and thioguanine (AAT).[4] In all, 29 of 44 patients (66%) treated with DAT and 9 of 9 patients treated with AAT had a complete remission (72% total). Median survival was 15+ months. Kantarjian and colleagues also recently reported the cases of 60 patients with APL who received either amsacrine- or anthracycline-based regimens.[5] The complete remission rate was 53% and the median duration of response was 29 months. Because of the limited size of our own patient population, we could not compare overall survival of APL patients with that of other AML subtypes. A recent large, prospective European study, however, showed no significant difference in survival between the APL patients and patients with other AML subtypes.[19]

Recommendations for DIC Therapy

On the basis of our experience, we propose the following treatment protocol be used in all patients with DIC associated with APL in whom induction chemotherapy is to be given (see Figure 3). Before administering any chemotherapy, heparin should be initiated with a bolus injection of 5,000 units followed by a constant infusion of 7.5 to 10 units per kg per hour (about half the usual dose for "full" anticoagulation).

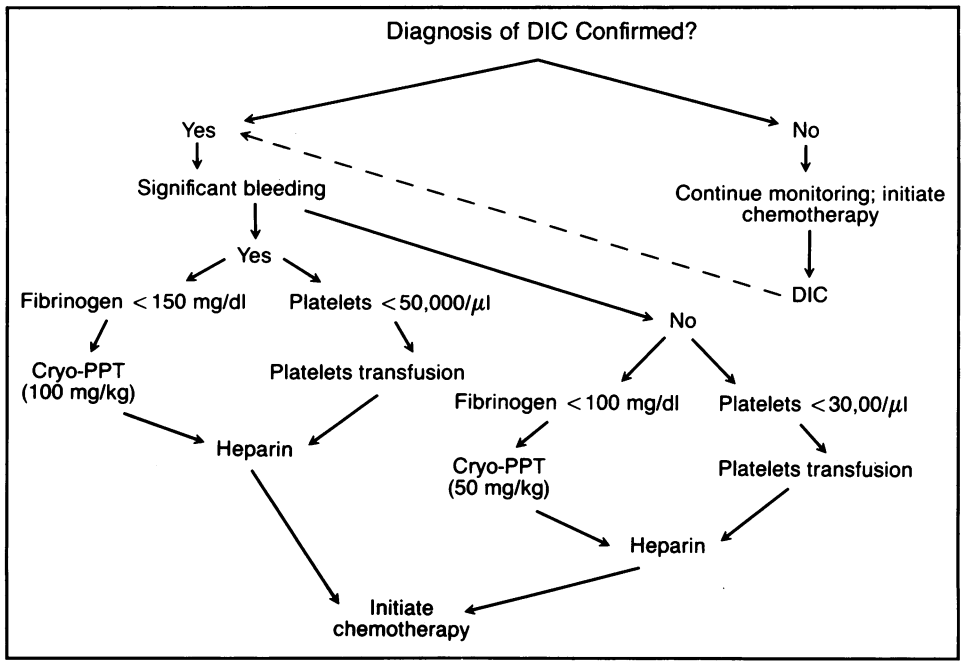

Figure 3.—The diagram shows an algorithm for the treatment of disseminated intravascular coagulation (DIC) in patients with acute promyelocytic leukemia. Where a diagnosis of DIC has been confirmed ("Yes"), most patients will have evidence of it at presentation. If not yet confirmed ("No"), coagulation variables must be monitored at least every 6 hours initially (see text). The heparin dose consists of 5,000 units initially, followed by 7.5 to 10 units per kg per hour, with the dosage adjusted as outlined in text. If bleeding continues after administering cryoprecipitates, platelet transfusion and heparin, a regimen of aminocaproic acid (Amicar) may be considered. Cryo-PPT = cryoprecipitate

Although there may be a transient excess prolongation of the prothrombin and partial thromboplastin times with the bolus, an "adequate" heparin effect will otherwise take several hours to achieve if no bolus is given. The heparin infusion should be adjusted to maintain the serum fibrinogen level above 100 mg per dl. If possible, this should be done without excessive prolongation of the PTT. Most patients will require escalation of the heparin dose towards "full" doses—that is, 15 to 20 units per kg per hour—as induction is initiated. This should be done as rapidly as possible with coagulation variables being measured at least every six hours initially.

Cryoprecipitate, which supplies predominantly fibrinogen and factor VIII, should be given before the heparin at a dose of 50 to 100 mg per kg if the initial serum fibrinogen level is less than 100 mg per dl and the patient is not bleeding significantly or less than 150 mg per dl if the patient is actively bleeding. Cryoprecipitate should continue to be given if heparin therapy alone does not maintain a fibrinogen level above 100 mg per dl. Platelet transfusions should be administered to maintain a platelet count of above 30,000 per μl. If a patient is actively bleeding, platelet counts should be maintained at greater than 50,000 per μl. An algorithm for the initial management of DIC is shown in Figure 3. In our experience, most patients will be adequately managed with heparin therapy without prolonging the PTT to more than 1.5 times the upper limit of the control range. In view of possible coexisting thrombocytopenia, extreme caution should be exercised when the PTT approaches this value as a result of giving heparin. Administration of cryoprecipitate and platelets may be required two to three times a day until the DIC comes under control.

For most cases, assaying the coagulation factors, such as factors V and VIII, is of little benefit. In addition, there is little role for the use of plasma as a source of factor replacement. Limited data suggest a possible therapeutic benefit from ϵ-aminocaproic acid.[20-22] Considering, however, the potential risk of thromboembolism associated with its use in cases of DIC, it must be used with caution in patients with APL.

Conclusions

In summary, although most patients with APL will have DIC, most can be successfully managed with the aggressive use of heparin plus platelet and cryoprecipitate transfusions as outlined above. The initial labeling index may help predict which patients are most likely to achieve a complete remission. Those patients who have a complete remission can be expected to have a survival comparable to responders with other AML subtypes. Finally, an anthracycline or amsacrine should be included as part of the induction chemotherapy regimen. Because marrow hypoplasia is not essential for complete remission, careful review is recommended before administering second or further courses of induction therapy.

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