Therapy-related myelodysplastic syndrome–acute myelogenous leukemia in patients treated for acute promyelocytic leukemia: an emerging problem

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The use of all-*trans* retinoic acid (ATRA) in combination with chemotherapy has markedly improved the prognosis for patients with acute promyelocytic leukemia (APL); the higher complete remission (CR) and survival rates now reported in this disease almost approach those obtained for other highly curable hematologic malignancies. Of 77 patients with APL who were consecutively treated at a single institution and who achieved CR after induction and consolidation therapy, 5 (6.5%) acquired therapy-related myelodysplasia (tMDS), acute myelogenous leukemia (AML), or both (tMDS–AML). Of these, 3 of 46 (6.5%) patients received front-line chemotherapy with or without ATRA and acquired tMDS–AML while in first remission of APL. Two underwent repeated chemotherapy cycles with ATRA because of APL relapse and acquired tMDS–AML while in the second or third remission of APL. In 2 patients, clinical and biologic characteristics of tMDS–AML were as expected for postalkylating forms (long latency, MDS phase preceding AML, karyotypic aberrations involving chromosomes 5 or 7), even though one of them had not previously received alkylating drugs. Three of the 5 patients died shortly after tMDS–AML diagnosis, one is alive with tMDS, and one is alive and in CR after allogeneic bone marrow transplantation. The occurrence of tMDS–AML after successful therapy for APL is an emerging problem. The availability of prognostic score systems at initial diagnosis and monitoring of residual disease by polymerase chain reaction might allow better tailoring of treatment intensity in APL to spare unnecessary toxicity and to minimize the risk for tMDS–AML in patients who are presumably cured. (Blood. 2002;99:822-824)

Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myelogenous leukemia (AML) that is characterized by peculiar clinical and biologic features. These include severe hemorrhagic diathesis at presentation, specific chromosome translocation t(15;17) resulting in the fusion of promyelocytic (PML) and retinoic acid receptor α (RARα) genes, and unique in vitro and in vivo responses to the differentiating agent all-*trans* retinoic acid (ATRA).[1-3] Front-line use of ATRA combined with chemotherapy has recently contributed remarkable improvement in the prognostic outlook of APL, converting this once frequently fatal leukemia to a highly curable disease.[4-12]

The development of therapy-related myelodysplasia or AML (tMDS–AML) after treatment for other tumors is one of the most serious complications occurring after chemotherapy for highly curable malignancies such as breast cancer, Hodgkin disease, non-Hodgkin lymphoma, and childhood acute lymphoblastic leukemia.[13-15] Among chemotherapy agents, alkylating drugs and topoisomerase II inhibitors such as anthracyclines and epipodophillotoxins have been frequently associated with the development of tMDS–AML. Regarding tMDS–AML occurring after treatment for APL, sporadic cases have been reported to date,[16-24] but no studies have investigated this issue by analyzing large series of patients. We report here our experience with the development of tMDS–APL in a consecutive group of 77 patients with APL treated at a single institution.

Patients, materials, and methods

Patients

Eighty-eight patients with APL consecutively diagnosed and treated at the Department of Cellular Biotechnology and Hematology of the University La Sapienza of Roma from January 1989 to September 1998 are included in this analysis. A minimum follow-up of 2 years after completion of induction therapy was considered for enrollment into the study. Diagnoses of APL were initially established by morphologic and cytochemical criteria following the French-American-British (FAB) guidelines[25] and were confirmed in all patients by Southern blot analysis, reverse transcription–polymerase chain reaction (RT-PCR), or both using specific primers and probes as described.[26,27]

Therapy for acute promyelocytic leukemia

Two consecutive protocols were used.

GIMEMA 0389. Twenty-eight patients who received diagnoses from January 1989 to March 1993 were randomly assigned to undergo induction treatment with idarubicin (IDA) alone (10 mg/m^2 for 4 days) versus IDA at the same dosage plus cytarabine (ARA-C) (200 mg/m^2 continuous infusion [c.i.] for 7 days).[28] Patients in complete remission (CR) were administered 3 polychemotherapy consolidation courses as reported.[4,28] At the end of consolidation, patients in CR were randomly assigned to undergo maintenance therapy with methotrexate (MTX, 15 mg/m^2 per week) and 6-mercaptopurine (6-MP, 90 mg/m^2 per day) for 2 years versus no further therapy.

AIDA protocol. Sixty patients given diagnoses from April 1993 to December 1998 underwent the AIDA regimen as reported.[4]

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Table 1. Main characteristics of patients at APL diagnosis and treatments administered

Patient no.	Sex/age, y	WBC ($\times 10^9$/L)	Platelets ($\times 10^9$/L)	PML/RARα Isoform	Front-line therapy*	Maintenance treatment	APL relapse	Salvage therapy for APL relapse
1	F/16	1.4	185	ND	GIMEMA 0389	MTX, 6-MP	No	No
2	F/52	1.5	12	BCR1	AIDA	ATRA plus MTX, 6-MP	No	No
3	M/63	6.3	99	BCR1	AIDA	ATRA plus MTX, 6-MP	No	No
4	M/35	43.7	30	ND	GIMEMA 0389	MTX, 6-MP	First	ATRA + CHT† + AuSCT‡
5	F/31	19.5	210	BCR3	AIDA	MTX, 6-MP	First Second	ATRA + CHT† + AuSCT‡ ATRA + CHT†

ND indicates not determined.
*As determined by RT-PCR. See "Patients, materials, and methods" for front-line treatment protocols GIMEMA 0389 and AIDA.
†Chemotherapy for APL relapse included mitoxantrone and cytarabine.
‡Southern blot analysis was used in these 2 patients to identify RARα and *PML* gene rearrangement.

Follow-up studies

Patients were monitored at regular time intervals after the end of consolidation therapy. Bone marrow samples were collected every 3 to 4 months and were analyzed by RT-PCR for PML–RARα amplification as reported elsewhere.[4,26] The diagnosis of tMDS–AML was established according to the FAB criteria.[29]

Cytogenetic analysis

Karyotypic analyses were carried out in marrow samples collected at the time of evolution in tMDS–tAML in all patients using direct technique and short-term culture (24 hours). The GTG banding method was used, and karyotypes were defined according to standard nomenclature.

Results

Of 88 consecutive patients with newly diagnosed APL, 8 died during induction, 2 died during consolidation therapy, one did not achieve molecular remission at the end of consolidation, and the remaining 77 (87.5%) obtained hematologic and molecular remission after induction and consolidation therapy. Five patients (3 of 53 or 5.6% in the AIDA 0493 study and 2 of 24 or 8.3% in the GIMEMA 0389 study) acquired tMDS–AML during follow-up. Initial clinical features and therapies for APL in these 5 patients are reported in Table 1. Patient 1 had been reported previously.[30] Three patients (patients 1-3) were in first CR when tMDS–AML was diagnosed, whereas 2 patients (patients 4-5) received further treatment for APL relapse before tMDS–AML developed, including alkylating agents as part of the conditioning regimen before autologous stem cell transplantation (AuSCT). Of the 2 latter patients, patient 4 received a diagnosis of tMDS–AML when in second CR, and patient 5 acquired tMDS–AML while in third CR. In all 5 patients, RT-PCR monitoring indicated molecular remission (ie negativity of the PML–RARα test) at the time of tMDS–AML diagnosis.

The main morphologic and karyotypic features of the tMDS–AML phase—time latency between APL and tMDS–AML diagnosis, treatment received for tMDS–AML, and patient outcomes—are reported in Table 2. In all patients, progressive pancytopenia was detected before diagnosis of tMDS–AML. A 2-month phase of tMDS preceded tAML diagnosis in patients 3 and 4. In patient 1, trilineage myelodysplasia was diagnosed concomitantly with tAML (FAB M4). Evolution into tAML was not detected in patients 3 and 5 (the latter underwent allogeneic SCT shortly after MDS diagnosis). Cytogenetic characterization revealed numeric abnormalities involving chromosome 5 or 7 in 2 patients (patients 2, 4), balanced t(10;11)(p14;q21) in patient 1, and a normal karyotype in patient 5, whereas it failed because of lack of evaluable metaphases in patient 3. In patient 1, the involvement of the *MLL* gene was ruled out by Southern blot analysis, as reported elsewhere.[30]

In light of poor performance status, 3 patients (patients 2-4) received only supportive care as therapy for tMDS. Of these, one is alive with tMDS 18 months after diagnosis of tMDS, and 2 died of progressive disease shortly after tMDS development. Patient 1 underwent reinduction and consolidation therapy followed by allogeneic SCT and died on day +50 from hepatic GvHD. Finally, patient 5, who acquired MDS in third CR, received supportive care for 5 months and then underwent allogeneic SCT. She is alive and in CR from APL or MDS 12 months after SCT.

Discussion

Since the advent of ATRA, APL is increasingly reported as curable.[4-12] Thus, larger numbers of long-term survivors of this disease are expected in the near future, and, as a consequence, more patients will be at risk for late complications related to antileukemic treatment. In fact, with few

Table 2. Clinical and biologic characteristics of the tMDS-AML phase and treatment outcome

Patient no.	Latency, mo	PML/RARα status*	tMDS phase (mo)	Karyotype	tMDS-AML treatment	Outcome
1	48	Negative	No	t(10;11)(p14;q21)	MTZ/AraC/VP16 allogeneic SCT	Died of GVHD (day + 50)
2	43	Negative	Yes (+ 18)	Monosomy 7	Supportive care	Alive in tMDS (at 18 mo)
3	46	Negative	Yes (2)	Failure	Supportive care	Died of disease progression (1 mo)
4	48 (33 from second CR)	Negative	Yes (2)	Del(5q−)	Supportive care	Died of disease progression (5 mo)
5	24 (2 from second CR)	Negative	Yes (5)	46xx	Allogeneic SCT	Alive in CR (+ 12 mo from SCT)

*By RT-PCR with 10^{-4} sensitivity.

exceptions,[31] conventional chemotherapy is still part of the protocol used in the front-line therapy for the disease. Furthermore, chemotherapy is considered essential to obtain sustained molecular remission, which in turn correlates with prolonged survival and potential cure.[1-3]

Current APL chemotherapy protocols usually include high-dose anthracyclines, mitoxantrone, and epipodophillotoxins—in other words, topoisomerase II inhibitors whose leukemogenic potential is well established.[32] All these agents were administered as part of the initial treatment in the 2 protocols reported in our study. In addition, 2 of the 5 patients described received further treatment with alkylating agents because of APL relapse. As reported in other tAML studies,[13-15] evolution from tMDS to overt tAML was rapid in 2 patients. However, we also observed a patient (patient 2) with a prolonged and indolent tMDS phase that lasted more than 18 months despite the fact that the tMDS clone harbored a poor prognostic aberration (monosomy 7). Interestingly, such a lesion would have led to a diagnosis of alkylating agent–related tMDS according to the World Health Organization (WHO) classification,[33] yet this patient was never administered alkylating drugs. The latter finding is in agreement with a recent report by Au et al,[24] who described a patient with APL treated without alkylating agents who acquired tMDS with chromosome 5 and 7 abnormalities. Together, these observations suggest that the pathobiologic associations proposed by the WHO to distinguish epipodophillotoxin-related from alkylating-related tMDS may not always hold true. Other clinical and biologic features of patients in our study were similar to those usually reported for tMDS–AML, with a median time latency of 46 months and evidence of unexplained pancytopenia and macrocytosis preceding tMDS diagnosis.

Three patients in the current study acquired tMDS while in prolonged first hematologic and molecular remission; 2 of them died, one of disease progression and the other of transplant-related toxicity. It is conceivable that these patients were cured of APL. Because studies have also suggested that a relevant proportion of patients with newly diagnosed APL are overtreated,[9,31,34] we emphasize the need for better tailoring of treatment intensity in this disease by identifying risk categories at diagnosis and by prospective minimal residual disease monitoring. Besides identifying patients at risk for relapse and in need of further treatment, the use of RT-PCR of PML–RARα during remission might spare the development of unnecessary toxicity in potentially cured patients.

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