PLENARY SESSION V
FRONT-LINE CLINICAL TRIALS

ROLE OF MAINTENANCE TREATMENT AFTER THE INTENSIVE CONSOLIDATION PROGRAM OF THE ORIGINAL AIDA PROTOCOL

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Background

The use of all-trans-retinoic acid (ATRA) in the treatment of acute promyelocytic leukaemia (APL) has greatly modified the prognosis of this peculiar subtype of leukaemia. However, it is still not clear whether or not a maintenance treatment is needed in consolidated APL patients in CR. In the pre ATRA era the GIMEMA study "LAP 0389" did not demonstrate any utility of a maintenance with 6-mercaptopurine associated to methotrexate in newly diagnosed APL patients using Idarubicin (as induction anthracycline) ± Cytarabine follow by three intensive consolidation courses.[1] However, after the introduction of ATRA two randomised studies have demonstrated that newly diagnosed APL patients have better results when receiving, after a consolidation program, ATRA ± chemotherapy as maintenance.[2,3] We report the mature results of the original AIDA (ATRA+Idarubicin) protocol in which newly diagnosed APL patients in molecular complete remission after the same three consolidation courses utilized in the previous GIMEMA study "LAP 0389"[1] were randomised to 4 maintenance strategies as those utilized in the European study.[3]

Methods

From July 1993 to May 2000, 807/828 newly diagnosed APL patients with molecular or cytogenetic evidence of t(15;17) received ATRA+Idarubicin (AIDA) as induction, followed by 3 intensive consolidation courses. Then , if RT-PCR negative for the PML-RARα fusion gene, they were randomised, as of 12/1997, into the following 4 arms: oral 6-mercaptopurine and intramuscular methotrexate (arm 1); ATRA alone (arm 2); 3 months of arm1 alternating to 15 days of arm 2 (arm 3); no further therapy (arm 4) according to the randomisation strategy of the European study.[3] After the first 318 patients randomised, starting from 01/1998, the remaining patients negative for the PML-RARα fusion gene at the end of consolidation were randomised only to arm 2 and 3 of the maintenance program. The duration of maintenance treatment was 2 years .

Results

Out of 807 patients evaluable for induction, 761 (94.30%) achieved CR, 44 (5.45%) died during induction and 2 (0.25%) were resistant to induction. The 1st, 2nd and 3rd consolidation courses were administered to 747, 728 and 681 patients respectively. Of these, 664 (97.5%) were evaluated for the PML/RARα fusion gene and 646 (97.3%) resulted RT-PCR negative for the presence of the PML-RARα hybrid gene and 586 (90.7%) were randomised to the maintenance program. In particular, before January 1998, 318 patients PML-RARα negative at the end of consolidation were randomised to receive 6-MP+MTX (arm 1); ATRA alone (arm 2); alternating chemotherapy and ATRA (arm 3); no further therapy (arm 4). The remaining patients negative for the PML-RARα fusion gene were randomised only to arm 2 and 3. The Kaplan-Meier estimated of EFS and OS of the 828 newly diagnosed APL patients were 70 % (C.I. 95%: 66.5-73.4) and 78% (C.I. 95%: 75.1-81.1) respectively. As for the 586 PML-RARα negative patients randomised to maintenance, the Kaplan-Meier estimated overall molecular DFS was 69% (C.I. 95%: 63.3-73.9) and did not reveal any statistical difference in the molecular DFS among the arms of randomization and the two overall molecular DFS obtained before or after 12/1997.

Conclusions

Newly diagnosed APL patients with confirmed t(15;17) treated with the original AIDA protocol who are RT-PCR negative for PML-RARα fusion gene at recovery from the intensive consolidation program , have no advantages from the addition of a maintenance program.

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TRIALS IN ACUTE PROMYELOCYTIC LEUKEMIA: THE MRC EXPERIENCE

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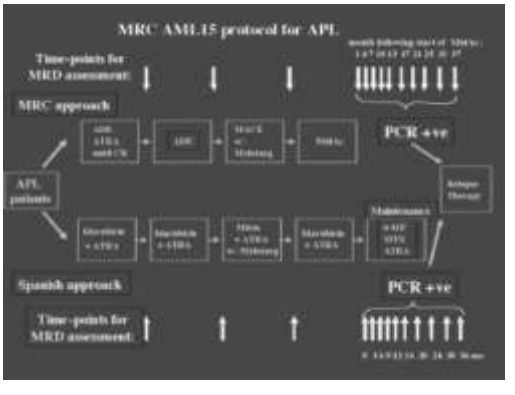
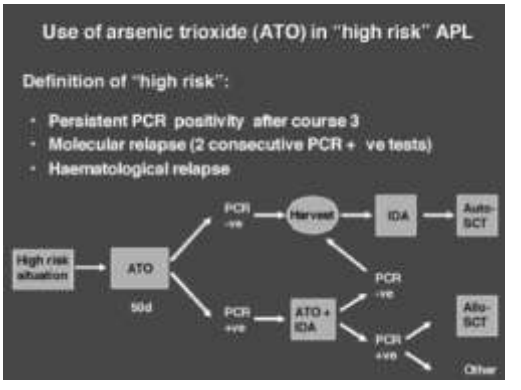
The MRC has incorporated the treatment of APL into its main trials (AML10 & 12) for Acute Myeloid Leukaemia. In 1988 patients received conventional induction chemotherapy and there was a possibility of allograft if a sibling donor was available, otherwise patients were randomised to four course of chemotherapy with or without autograft. In 1991 we introduced ATRA to the trial. Patients were randomised to receive either to receive a short (day) course or daily dosing until morphological CR was obtained. The rationale of only giving a short course was that the previous experience was that early bleeding attributed to the expected coagulopathy was the main cause of treatment failure in the first few months, and that the use of ATRA could prevent that, and will limit the risk of developing RAS. No maintenance treatment was given. In the AML12 trial patients received standard chemo with simultaneous ATRA till remission. Four hundred and fifty APL patients entered these trials but only 3% were > 60years. Most had cytogenetic confirmation of the t(15:17), but some were confirmed molecularly only. The survival of these two groups was the same. Trisomy 8 was present in 13% of patients as the most frequent additional abnormality, but this did not adversely affect prognosis. The overall survival at 5 years was 69%, and 77% of patients presented with a WBC $<10\times10^9$/L. Long ATRA was significantly superior, having a 5 year survival of 80%, and thereafter was adopted as standard treatment. The reason that there was a major negative impact of WBC>10 was the difference in induction deaths (24% vs 5% p=0.0001).This resulted in a poor survival (54%). We tested the Spanish- Italian prognostic combination of WBC<10with platelets below or above 40×10^9/L, and a WBC>10. The respective CR rates were 89%, 92% and 74%. Subdivision of the low count patients based on platelet count was not prognostic in this dataset, which were probably more intensively treated. Overall only patient age and presenting WBC were validated as prognostic factors. Patients were routinely monitored by RT-PCR with a sensitivity of 1 in 10^4. The most relevant time point in these studies was the residual positivity after consolidation when the risk of relapse was 56% for those who were +ve and 26% for those who were –ve. However the majority of patients were PCR negative at this point and the majority of subsequent relapses came from patients who were negative at this point. In the pre-ATRA cohort, transplant significantly reduced relapse to a greater extent that seen with the other favourable groups. The current AML15 Trial compares our standard chemotherapy combined with ATRA against the protocol devised by the Pethema group. In addition patients are randomised in course 3 to receive Mylotarg (3 mg/m^2) on day 1.



The primary endpoints are resource use and quality of life, with response and survival as secondary endpoints. Patients are intensively monitored by RQ-PCR for up to 3 years. So far all of the 157 patients entered have been screened and 90% of patients have had PCR follow-up. Patients who remain molecularly +ve at the end of treatment, who become +ve having been –ve, or who have a haematologically relapse are offered further treatment with Arsenic Trioxide (ATO) in one of 2 schedules, either daily in a dose of 0.15mg/kg/day or with a loading dose of 0.30mg/kg for 5 days followed by 0.25mg/kg X2 per week. Consolidation for those who re-enter morphological CR will be auto (for molecularly –ve patients) or allograft (for those who remain +ve).



The preliminary results so far show the overall the overall survival for both arms combined is 92% at 2 years, which appears superior to the previous AML12 outcome (77%). Seventy–four have so far been randomised to Mylotarg in course 3 with no evidence of excess toxicity. The survival from this randomisation is currently 100%.

Preliminary experience of the ATO option in a small number of patients, mostly in patients not in the AML15 trial indicates that each schedule results in a similar CR rate.

USE OF ATRA AND ARSENIC TRIOXIDE WITHOUT CHEMOTHERAPY (LOW-RISK PATIENTS), OR WITH ONLY INDUCTION CHEMOTHERAPY (MYLOTARG) (HIGH-RISK PATIENTS) IN UNTREATED ACUTE PROMYELOCYTIC LEUKEMIA

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The general success encountered in treating patients with newly- diagnosed APL masks two problems in the management of this disease.[1] First, cure rates in patients with pretreatment WBC counts > 10,000/μL (high-risk patients) are only about 70%, in contradistinction to rates of 90% in low-risk patients. Second, although older patients (e.g. age > 60) comprise only a minority of those with APL, these patients not infrequently develop serious, and occasionally fatal, infections consequent to the myelosuppression associated with use of anthracylines +/- ara-C, for example in *consolidation therapy*.[2] Currently high-risk patients presenting to M.D. Anderson with untreated APL receive ATRA, arsenic trioxide (ATO), and gemtuzumab ozogamycin (hereafter mylotarg) in an attempt to improve their cure rate. Low-risk patients receive ATRA + ATO. Here the objective is to avoid the use of chemotherapy. Thus, chemotherapy (mylotarg) is given only if molecular remission is not obtained or if relapse (molecular or clinical) is observed. Before proceeding to a discussion of our current results with this program, I will describe the steps that motivated its adoption.

Chemotherapy is not needed to cure APL: the liposomal ATRA (L-ATRA) trial

It is generally thought that, oral ATRA, although highly effective in inducing CR, cannot cure APL,[3,4] although documentation of the latter belief is not easy to obtain, 10-15 years ago, a pharmacologic explanation for the development of resistance to ATRA was in vogue. Specifically, it was postulated that repeated exposure to ATRA resulted in accelerated hepatic metabolism and thus the observed decline in serum tretinoin concentrations. Because of its encapsulation in liposomes, L- ATRA could be given intravenously. Such parenteral administration avoided the first pass elimination of ATRA by hepatic enzymes; indeed, the ability of L-ATRA to maintain serum tretinoin concentrations (and to reach higher concentrations) than was possible with oral ATRA was readily demonstrable. This led to a trial in which we administered L-ATRA to untreated patients, with the intent to add idarubicin only for molecular failure, as described for the current ATRA + ATO trial. The salient observation was that 10/26 patients presenting with a WBC count <10,000/μL have remained in continuous remission for a median of 5-6 years despite never receiving therapy other than L-ATRA.[5] L-ATRA cured 0/8 high-risk patients. Age, presenting WBC or platelet count, or type PML-RARα isoform did not distinguish which low-risk patients would be cured. Average survival seemed similar to that we had previously observed with oral ATRA + idarubicin induction followed by idarubicin consolidation and 2 years of idarubicin and POMP (6 MP, methotrexate, vincristine, and prednisone) maintenance, although these historical patients did not receive ATRA during either consolidation or maintenance. This similarity in survival suggested that, despite the lack of sensitivity of PCR testing for detecting residual disease, a strategy in which chemotherapy was administered only after failure of treatment that did not include chemotherapy, was feasible. Furthermore, the L-ATRA experience suggested that chemotherapy was not necessary to cure untreated APL.

Effectiveness of mylotarg in APL

L-ATRA became unavailable after 1999. Our next study was influenced by Jurcic et al's report that the anti CD33 antibody HuM195 could produce PCR negativity in patients in hematologic CR.[6] This seemed logical enough since a high proportion of patients with APL are not only CD33 *positive*, but that APL cells are rich in CD33. Accordingly, we administered mylotarg (an anti CD33 antibody conjugated to the cytotoxic agent calicheamicin) together with ATRA,[7] treating 11 low–risk patients and 7 high-risk patients. Once in CR patients were to receive 7 courses of mylotarg at the induction dose of 9 mg/m^2 on day1 + ATRA, on a 2 weeks on- 2 weeks off schedule. As in the L-ATRA trial, PCR testing was done every 3 months for 1-2 years, with idarubicin added for molecular, as well as hematologic/extramedullary failure. All 11 low risk patients entered CR, and 9 remain alive in CR with a median follow-up of 137 weeks. Mylotarg was tolerated as idarubicin; thus, there was no more difficulty in administering the planned number of post-remission course than with idarubicin. Comparison of event free survival in low-risk patients with that seen in the historical patients described above revealed superiority for mylotarg + ATRA. Although conventional statistical significance was not reached and recalling that the historical patients did not receive ATRA in CR (but were treated for 2 years), we nonetheless believed that it was very unlikely that mylotarg + ATRA was inferior to idarubicin + ATRA. This view together with the success reported by Lo Coco *et al.*[8] with mylotarg in treatment of molecular relapse prompted us to adopt this drug as our standard chemotherapeutic agent in APL.

ATRA + ATO +/- Mylotarg in APL: General Considerations

Reports from India[9] and Iran[10] have noted the effectiveness of ATO in untreated APL. Of particular interest to us is Shen et al's trial [4] randomizing untreated patients to ATRA, ATO, or ATRA + ATO. In remission patients continued to receive the originally assigned arm but were also given chemotherapy. The greatest reduction in the level of pre-treatment PML-RARα transcripts at time of CR occurred in patients given ATRA + ATO. Given that addition of ATRA to ATO did not increase toxicity, it appears that the optimal non-chemotherapy regimen to investigate in untreated patients is ATRA + ATO. Our trial differs from the Chinese trial as follows:[1] low-risk patients do not receive chemotherapy (mylotarg) unless 2 consecutive PCR tests performed 2-4 weeks apart at a sensitivity level of10^{-4} beginning 3 months from CR date are positive[2] high-risk patients receive mylotarg 9 mg/m^2 on day 1 of treatment , but thereafter are managed identically to low-risk patients, and[3] ATO begins 11 days after the first dose of ATRA rather than simultaneously. The decision to give mylotarg to high-risk patients reflected the poor results with L-ATRA monotherapy in such patients, as described above. Administration of ATO was delayed to prevent hepatotoxcity; none has been seen however and a revised version of the protocol would call for ATRA and ATO to begin concurrently. Is it ethical to use ATRA+ATO, while reserving chemotherapy in low-risk patients given that the cure rate of such patients is > 90% with standard ATRA+idarubicin? An answer to this question requires consideration of the ATRA+ATO trial's statistical design. Thus, the design operates such that if the true CR rate with ATRA+ATO is only 60%, rather than our historical 80%, the expected median sample size is 18. However, given our accrual rate, 21 patients would be expected to have received ATRA+ATO by the time accrual is stopped. 60% of these 21 would get a CR compared to 80% of the 21 with historical treatment. Thus the cost of conducting the trial is (80%×21) – (60%× 21) = 4 patients. If the true CR rate with ATRA + ATO is below 60% the trial is designed to stop earlier, leading to the same cost. Whether this poten-

tial cost is worth discovering the potential utility of ATRA + ATO was the question we answered affirmatively before beginning the trial.

ATRA+ATO+/-Mylotarg in APL: Results as of 6/22/05. 23 consecutive low-risk patients have been treated. Their median age is 46, median WBC 1,300/μL; 7 have had platelet counts > 40,000/ μL, thus being regarded as *intermediate-risk* by Sanz *et al.,*[11] 21 of the 23 (91%; 95% confidence interval 72-99%) have entered CR. As seen in Table 1, all 21 patients remain in hematologic and molecular CR. The median duration of hematologic CR is 14 months (with 4 patients having been followed for at least 2 years) and that of molecular CR is 12 months (with 3 patients having been followed for at least 2 years). 18 of 22 high-risk patients presenting since the protocol opened have received chemotherapy + ATRA + ATO; the exceptions were ineligible because of pregnancy (2 patients), hyperbilirubinemia, or an arrhythmia.

Table 1. Duration of Hematologic and Molecular CR in 21 Patients with WBC < 10,000/μl Given ATRA + ATO.

Duration Molecular CR (months)	Duration Hematologic CR (months)
12+	25+
32+	32+
26+ (a)	26+
27+	27+
23+	23+
18+	18+
7+ (b)	9+
12+	15+
17+	17+
13+	13+
11+ (c)	14+
15+	15+
11+	11+
11+	14+
13+	13+
10+	10+
6+	6+
6+	6+
4+	6+
0	2+
0	0

(a) ATO replaced by mylotarg in CR because of long QTc interval; (b) ATO replaced by mylotarg in CR because of atrial arrhythmia; (c) ATO replaced by mylotarg in CR because of ventricular arrhythmia

The 18 had a median WBC of 32,000/μL (up to 131,000/μL). I4 received mylotarg as chemotherapy, 2 mylotarg + idarubicin, 1 idarubicin, and 1 no chemotherapy. CR rates were 11/14 (79%, 95% CI 49-95%), 2/2, 1/1, and 1/1 respectively. All 3 patients who did not achieve CR did not receive ATO: 1 presented with CNS hemorrhage and died on day 2 (recalling that ATO was to begin on day 11), 1 presented with a cerebral infarct and died on day 17, and 1 died on day 3. Two issues related to these results are worth mentioning. First, it would appear reasonable, at least in such patients, to begin ATO on day 1. Second, it is unclear whether patients, such as ours, presenting with CNS pathology are typically registered on APL studies. Clarification of this question might explain discrepancies in CR rates among different studies. Table 2 depicts outcome in CR in high-risk patients. One relapse has been observed in the 11 patients who achieved CR following therapy with ATRA+ATO+ mylotarg. This patient became PCR positive 1 year from CR date and, despite addition of mylotarg, had a CSF relapse 3 months later, with the marrow remaining PCR positive. The 10 patients remaining alive in CR have had a median molecular follow-up of 13 months and a median hematologic follow-up of 15 months. Three patients remain in molecular remission for 2-3 years.

Table 2. Duration of hematologic and molecular CR in 15 patients with WBC > 10,000/mL given induction chemotherapy+ATRA+ATO.

Chemotherapy during induction	Duration molecular CR (months)	Duration hematologic CR (months)
Mylotarg	33+	33+
Mylotarg	24+	27+
Mylotarg	12 RELAPSE	15 RELAPSE
Mylotarg (a)	24+	24+
Mylotarg	15+	18+
Mylotarg (b)	19+	19+
Mylotarg	11+	12+
Mylotarg (c)	9+	9+
Mylotarg	6+	9+
Mylotarg	6+	7+
Mylotarg	6+	6+
Mylotarg and Idarubicin	9 RELAPSE	10 RELAPSE
Mylotarg and Idarubicin	22+	22+
Idarubicin	37+	37+
None	3+	3+

(a) ATO replaced by mylotarg in CR because of neuropathy; (b) ATO replaced by mylotarg in CR because of atrial arrhythmia;(c) 25% reduction in ATO dose because of atrial arrhythmia.

Essentially all patients are PCR positive when CR is achieved, including those in whom the marrow PCR is examined when blood counts have met the criteria for CR. However, 31/31 patients examined 2-4 months from CR date have been PCR negative, including 18 patients who because they were low-risk received only ATRA + ATO.

Table 3 depicts results according to WBC and FLT 3 status. Not surprisingly, there is an association between FLT3 aberrations and WBC > 10,000/μL. However to date the presence of a FLT3 aberration has not appeared to convey a worse prognosis.

Table 3. Results by FLT3 Status and WBC.

	Flt 3 negative	Flt3 ITD or mutation
WBC <10	10 pts, 10 CR, 0 relapses, median dur CR 16 mos	4 pts, 3 CR, 0 relapse , median dur CR 10 mos
WBC > 10	1 pt, 1 CR, relapse at 12 mos	4 pts, 4 CR, 0 relapses, median CR 14 mos

The most noteworthy toxicity observed has been arrhythmias in patients receiving ATO. As indicated in tables 1 and 2, mylotarg has been substituted in CR for ATO solely because of cardiac events in 5 patients (arrhythmias in 4, long QTc interval in 1), with the dose reduced 25% in a 6th also because of an arrhythmia. In 3 cases the arrhythmias were asymptomatic and in 2 were only unclearly related to symptom. None of the 6 patients had electrolyte abnormalities or histories of heart disease. Race appears to be the principal predictor of arrhythmia development.Thus, both blacks in the study have had arrhythmias contrasted with 3 of the 36 whites given ATO (p=0.01). Westervelt *et al.,* have noted a predisposition for fatal arrhythmias among blacks[12] Two patients have developed melanoma while receiving ATO + ATRA. Figure 1 compares event-free survival time (EFST) in low-risk patients according to whether they received ATRA + mylotarg for induction and in CR or ATRA

+ ATO for induction and in CR. Duration of therapy in CR was similar (6-8 months). Assuming that ATRA + mylotarg is therapeutically equivalent to ATRA + idarubicin (see above), the similarity in EFST between ATRA + mylotarg and ATRA + ATO suggests that is feasible to omit chemotherapy in such patients. Similarly, the data in table 2 suggest that ATRA + ATO + a single course of mylotarg during induction may be useful in high-risk patients. The U.S. Intergroup plans to test this hypothesis by conducting a single arm trial using the M.D. Anderson induction regimen, but also including therapy with mylotarg during consolidation.

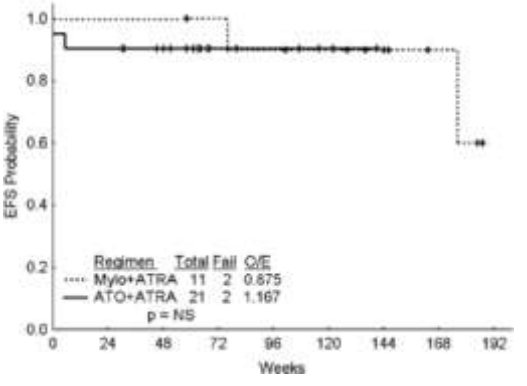

Figure 1. Event-free survival in patients with WBC counts < 10,000 according to whether they received ATRA + mylotarg (dotted line) or ATRA + ATO (solid line). There are 11 patients in the former group [median WBC count 1300, median age 54, median platelet count 38,000, Sanz intermediate risk (11) 5 patients].; there have been 2 events and the median censoring time is 139 weeks. There are 21 patients in the latter group [median WBC count 1400, median age 45, median platelet count 23,000, Sanz intermediate risk 5 patients]. There have been 2 events and the median censoring time is 61 weeks.

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TREATMENT OF NEWLY DIAGNOSED ACUTE PROMYELOCYTIC LEUKEMIA WITH ATRA AND INTENSIFIED DOUBLE INDUCTION THERAPY: RESULTS OF THE GERMAN AML COOPERATIVE GROUP

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Introduction

Intensive chemotherapy is essential to stabilize complete remission induced by all-trans retinoic acid (ATRA), and to achieve cure in patients with newly diagnosed acute promyelocytic leukemia (APL). This observation indicates the importance of an efficient chemotherapy for combination with ATRA.

The chemotherapy strategy of the German AML Cooperative Group (AMLCG) for newly diagnosed acute myeloid leukemia (AML) including APL (randomized AML-86 protocol) consisted of a double induction therapy with standard (TAD/TAD), or high dose ara-C (TAD/HAM), followed by TAD consolidation and three years monthly maintenance chemotherapy.[1] This strategy proved highly effective in the subgroup of patients with APL. The three and ten year relapse free survival rates of APL patients were 59% and 47%, respectively, with a significant benefit of the high dose ara-C arm (p=0.02).[2]

The present prospective multicenter study for patients with newly diagnosed APL (APL 1994 Study) was initiated with the intention to combine the positive effects of the differentiating substance ATRA with a chemotherapy strategy of proven high curative potential. Induction therapy consists of ATRA in combination with the more efficient arm of the previous chemotherapy protocol (TAD/HAM induction, consolidation and maintenance chemotherapy). Monitoring of minimal residual disease by RT-PCR of PML/RARα transcripts is mandatory in order to assess quality and stability of remission on the molecular level.

Study design

Induction therapy consists of TAD/HAM double induction chemotherapy and the simultaneous administration of 45 mg/mÇ ATRA daily until complete hematological remission or for a maximum of 90 days. The HAM course is given on day 21 after the start of TAD independently on cytopenia. Two to four weeks after CR, one consolidation course of TAD is given followed by three years cyclic monthly maintenance chemotherapy (Figure 1).

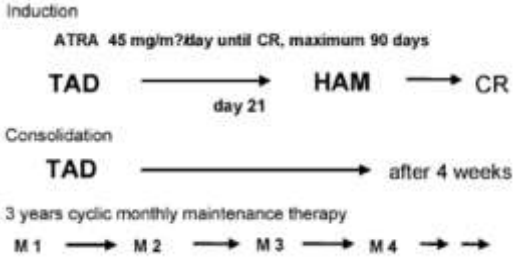


Figure 1. Treatment plan of the APL94 Study of the German AMLCG..

Patients older than 60 years receive a less intensive induction chemotherapy: The second induction cycle (HAM with reduced ara-C dose of 1 g/m^2 instead of 3 g/m^2) is only given, if complete remission was not achieved after the first cycle (Table 1). Molecular monitoring of PML/RARα is scheduled after induction, after consolidation and every three months during maintenance therapy. In the case of persistence or reappearance of PCR-positivity for PML/RARα after consolidation or during maintenance, patients are to undergo allogeneic bone marrow transplantation (BMT), if a related donor is available.

Patients not eligible for BMT receive 45 mg/m^2 ATRA over 7 days in addition to the chemotherapy in each maintenance course.

Table 1. Chemotherapy.

TAD	ara-C	100 mg/m? i.v.	day 1+2
		2x100 mg/m? i.v.	day 3-8
	daunorubicin	60 mg/m? i.v.	day 3-5
	6-thioguanine	2x100 mg/m? p.o.	day 3-8
HAM	ara-C	2x3 (1*) g/m? i.v.	day 1-3
	mitoxantrone	10 mg/m? i.v.	day 3-5
cyclic monthly maintenance	ara-C in combination with	2x100 mg/m? s.c.	day 1-5
M1	daunorubicin	45 mg/m? i.v.	day 3+4
M2/M4	6-thioguanine	2x100 mg/m? p.o.	day 1-5
M3	cyclophosphamide	1000 mg/m? i.v.	day 3

* 1 g/m?ara-C in patients aged over 60 years

Results

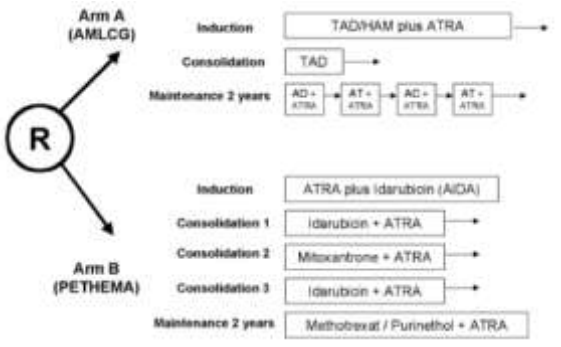
The present study for newly diagnosed APL represents the first one, in which induction chemotherapy in combination with ATRA is intensified by high doses of ara-C. It should be emphasized that the induction chemotherapy is not only intensified by high dose ara-C but also by the early application of the second induction cycle after an interval of 21 days independent on the recovery of blood counts. The patients' data were routinely updated every half year and presented at the meetings of the German AMLCG since the start of the APL study in 1994. A new update (August 2005), now including data of more than 170 patients, will be shown at the 4th International Symposium on Acute Promyelocytic Leukemia scheduled for September/October 2005 in Rome.

The summarized results of earlier reports of the present study indicate the high antileukemic efficacy of high dose ara-C and its importance in APL: [2-5]

- with the AMLCG strategy including high dose ara-C and ATRA during induction therapy a low relapse rate in all 'risk groups' of APL was seen;
- the initial WBC count is only a borderline risk factor for relapse;
- poor prognosis might be improved by the rapid reduction of the malignant clone (molecular remission in 90% after 6 to 8 weeks),
- no CNS relapses were observed in the present AMLCG study so far;
- high dose ara-C in APL proved highly effective in the pre-ATRA era (AML-86: RFS 70% vs. 19%, p=0.02).

Future perspectives

In the subsequent study (APL 2005 Study) of the German AMLCG, the concepts of the AMLCG and of the Spanish PETHEMA group will be randomly compared (Figure 2).[6] The study will be started as a pilot study to compare the kinetics of the minimal residual disease in both treatment arms with qualitative nested PCR and quantitative REAL-time PCR. The study also enables the integration in a common European APL concept offering the PETHEMA arm as a reference arm for an upfront randomized comparison of several treatment strategies.



Molecular Monitoring of minimal residual disease is mandatory.

Figure 2. Treatment Concept of the APL 2005 Study of the German AML-CG. Randomization between the AMLCG and PETHEMA strategies.

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A RANDOMIZED STUDY WITH OR WITHOUT MAINTENANCE/INTENSIFICATION CHEMOTHERAPY IN NEWLY DIAGNOSED PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA: THE JALSG APL97 STUDY

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In newly diagnosed APL, all-*trans* retinoic acid (ATRA)-combined chemotherapy improves clinical outcome compared with chemotherapy alone, but the significance of maintenance/intensification chemotherapy remains unclear.[1,2] In APL97 study, we randomized the patients whose minimal residual disease (MRD) was negative at the end of consolidation to either observation or maintenance/ intensification therapy. This will also answer whether MRD-detection using RT-PCR is useful for the signals to discontinue further chemotherapy in APL.

Eligibility

Eligible criteria are as follows: newly diagnosed APL, age ranged from 15 to 70 years old, PS 0 to 3, sufficient function of heart, lung, liver and kidney, and informed consent. Diagnosis of APL was made according to the FAB classification and the presence of t(15;17) and/or the PML-RARA fusion transcript.

Remission Induction Therapy

Patients receive 45 mg/m^2 of ATRA orally daily until the day before the start of first consolidation therapy, if they have leukocyte counts below 3.0×10^9/L and APL cells below 1.0×10^9/L at the start of therapy (Group A). ATRA at the same dosage combined with idarubicin (IDR) 12 mg/m^2/day for 2 days (30-minute infusion) and cytarabine (Ara-C) 80 mg/m^2/day for 5 days (continuous infusion) are administered in patients who have initial leukocyte counts between 3.0×10^9/L and 10.0×10^9/L, or initial leukocyte counts below 3.0×10^9/L and APL cells 1.0×10^9/L or more (Group B). Patients who have initial leukocyte counts 10.0×10^9/L or more receive IDR 12 mg/m^2/day for 3 days and Ara-C 100 mg/m^2/day for 5 days in addition to ATRA (Group C). Patients who show blast and promyelocyte counts in the peripheral blood higher than 1.0×10^9/L during the treatment with ATRA are scheduled to receive additional cycle of chemotherapy consisted of IDR 12 mg/m^2 for 2 days and Ara-C 80 mg/m^2 for 5 days (Group D). Coagulopathy is treated in accordance with the prophylaxis for bleeding.

Consolidation therapy

After achieving complete remission (CR), patients receive 3 different courses of consolidation chemotherapy. The first consolidation consisted of mitoxantrone (MIT, 7 mg/m^2, 30-minute infusion) for 3 days and Ara-C (200 mg/m^2, continuous infusion) for 5 days. The second consolidation consisted of Ara-C (140 mg/m^2) for 5 days, etoposide (ETP, 100 mg/m^2, 1-hour infusion) for 5 days, and daunorubicin (DNR, 50 mg/m^2) for 3 days. The third consolidation consisted of Ara-C (140 mg/m^2) for 5 days and IDR (12 mg/m^2, 30-minute infusion) for 3 days.

Maintenance/Intensification therapy

After completion of consolidation therapy, patients who show absence of PML-RARA transcripts are randomized to receive 6 courses of maintenance/intensification therapy every 6 weeks or observation alone. The patients showing presence of PML-RARA transcripts at the end of consolidation therapy are scheduled to receive late ATRA therapy followed by maintenance/intensification therapy, and also plan

to receive allogeneic stem cell transplantation if they have an HLA-identical donor. The first course consisted of bephenoyl cytarabine (BHAC, 170 mg/m^2, 2-hour infusion, day 1 through 5), DNR (30 mg/m^2, 30-minute infusion, days 1 and 4) and 6-mercaptopurine (6MP, 70 mg/m^2, orally, days 1 through 7). The second consisted of BHAC and MIT (5 mg/m^2, 30-minute infusion, days 1 and 2). The third consisted of BHAC, ETP (80 mg/m^2, 1-hour infusion, days 1, 3, and 5) and vindesine (VDS, 2 mg/m^2, bolus infusion, days 1 and 8). The fourth consisted of BHAC, aclarubicin (ACR, 14 mg/m^2, 30-minute infusion, days 1 through 4) and 6-MP. The fifth and sixth courses were the same as the first and third, respectively.

Late ATRA therapy

Patients showing MRD at the end of consolidation therapy receive late ATRA therapy prior to maintenance/intensification therapy. For the late ATRA therapy, patients receive 45 mg/m^2 of ATRA orally after meals daily for 4 weeks.

Laboratory examinations

The PML/RARA fusion transcripts in bone marrow samples were analyzed by RT-PCR at the diagnosis, after the induction, consolidation, and maintenance/intensification therapy. The detection limit of PML/RARA transcripts was 10-4.

Results

A total of 294 evaluable patients were registered from May 1997 to June 2002. Median age was 48 years old (15 to 70) and 278 of 294 (94%) patients obtained CR. CR was achieved 94%, 97%, 89% and 96%, in Group A, B, C, and D, respectively. Induction failure was due to bleeding (4%), pneumonia (0.3%) and RA syndrome (1%). Predicted 6-year overall and event-free survivals (EFS) were 81% and 65%. EFS in Groups A, B, C and D were 74, 64, 54 and 62%, respectively (p=0.0675). Negativity of PML-RARA transcripts were observed in 94% of patients who accomplished consolidation chemotherapy, and 182 patients were randomized with or without maintenance/intensification therapy. No difference in DFS was observed between two groups (p=0.3718).

Discussion

We did not find any benefit in adding maintenance/intensification chemotherapy in APL patients who were MRD-negative after consolidation therapy. Increased risk of relapse was identified in patients with higher leukocyte counts, who would benefit from additional therapies such as arsenic as well as chemotherapy. Although it remains unclear whether all patients need cytotoxic drugs to obtain CR, our study shows that patients with low leukocyte counts at diagnosis achieved a favorable outcome in spite of ATRA alone for induction therapy. Thus the stratified induction therapy might have a merit to lower therapy-related toxicities. From May 2004, we are conducting a randomized phase III study (APL204) for newly diagnosed APL to compare ATRA and Am80, a new synthetic retinoid which has more potent and favorable PK/PD than ATRA, for maintenance therapy to MRD-negative patients at the end of consolidation chemotherapy.

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RISK-ADAPTED TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA: UPDATED RESULTS OF THE SPANISH PETHEMA TRIALS USING ATRA AND ANTHRACYCLINE MONOCHEMOTHERAPY

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Through the combination of all-trans retinoic acid (ATRA) and chemotherapy, cure is now a reality for most patients with acute promyelocytic leukemia (APL). In fact, several modern approaches based on this combination have led to prolonged disease-free survival and potential cure for more than 80% of patients achieving complete remission. The current consensus on the most appropriate induction therapy, once a diagnosis of APL has been confirmed at the genetic level, consists of the simultaneous administration of ATRA and anthracycline-based chemotherapy.[1,2] The choice of anthracycline and whether it should be combined with other agents, such as cytosine arabinoside, remain controversial. Exceptions to the use of anthracycline-based induction regimens should be considered only for individual patients in whom chemotherapy is contraindicated. This is the case of patients with certain clinical conditions such as severe organ failure, anticoagulant therapy, very elderly patients (more than 80 years old), and others, in whom the toxicity of intensive chemotherapy is often unacceptable. For these cases, arsenic trioxide (ATO) has recently emerged as a suitable alternative.[3] However, there is not the same degree of consensus on the most appropriate consolidation therapy, except for giving at least two or three cycles of anthracycline-based chemotherapy. Apparently, therapeutic efficacy did not differ according to the number of cycles and type of drugs combined with anthracyclines. Using less intensive monochemotherapy with anthracyclines for both induction and consolidation therapy, which led to a significant reduction in treatment-related toxicity during the consolidation phase and a high degree of compliance, the LPA96 study of the PETHEMA group reported outcome results similar to those obtained in other major studies using anthracycline-based chemotherapy combinations. Given the common therapy backbone and the similar outcome results of their respective trials, both the GIMEMA and PETHEMA groups carried out a joint study that defined a simple model for relapse prediction based on the initial white blood cell and platelet counts. Based on this study, the GIMEMA and PETHEMA groups decided to apply this predictive model to design their next studies, thereby adopting a risk-adapted strategy. In November 1999, aiming to improve the antileukemic efficacy in patients with increased relapse risk, the PETHEMA started the new trial LPA99 based on a risk-adapted strategy. The results obtained in 426 consecutive patients with newly diagnosed PML-RARα positive APL who were enrolled in these two consecutive studies (LPA96 and LPA99) have been recently reported in Blood.[5] This study, which was recently updated including a significantly higher number of patients and longer follow-up than in the first report,[6] shows that combining ATRA with anthracycline monochemotherapy for induction and consolidation, followed by ATRA and low dose methotrexate and mercaptopurine for maintenance therapy, results in extremely high antileukemic efficacy, moderate toxicity and a high degree of compliance in patients with APL. The novel addition of ATRA to consolidation therapy, combined with a moderate increase in the dose of anthracycline for intermediate- and high-risk patients, resulted in higher antileukemic activity with no additional severe toxicity. Overall, 665 patients, ranging from 2 to 83 years of age, were eligible for AIDA induction from November 1996 to December 2004.

Remission induction rates were similar in both LPA96 and LPA99 trials, 89% and 91%, respectively. These results confirm the virtual absence of drug resistance. It should be noted that the 4 cases labeled as resistant leukemia were evaluated too early for response, between the days 19 and 33 after completion chemotherapy. Today, it is well known that a proportion of patients need up to 40 or 50 days to complete terminal differentiation of blasts. The two major causes of failure were bleeding and infection, accounting for around 5% and 3%, respectively. No impact was observed in the mortality rate due to hemorrhage according to the use of antifibrinolytic prophylaxis with tranexamic acid nor in the morbidity and mortality rate associated to the retinoic acid syndrome according to the use of prednisone prophylaxis.

Regarding post-remission outcome of patients treated with the currently ongoing risk-adapted protocol (LPA99), 8 patients died in remission. It should be noted that only one of these patients was young. This 33-year old patient, who had had a cerebral hemorrhage during induction therapy, died 18 months later, during maintenance therapy, due to an epileptic status. Other post-remission events were two molecular persistences, 7 molecular relapses and 19 clinical relapses, including 5 in central nervous system. It should be noted that 4 CNS relapses occurred among 94 high-risk patients and only 1 among the remaining 351 patients at risk. Overall, these results translate into a 5-year disease-free (DFS) and relapse-free survival (RFS) of 89% and 91%, respectively. The 5-year cumulative incidence of relapse (CIR) is 9%. These estimates still show significant differences according to WBC count. DFS and RFS at 5-years in patients with less than 10 thousand leukocytes were 93% and 95%, respectively, with a CIR of 5%. In contrast, patients with more than 10 thousand leukocytes at presentation have a CIR at the same time point of 22%. In conclusion, this updated analysis on a large series of patients with APL confirms that a risk-adapted strategy combining ATRA and anthracycline monochemotherapy provides a high antileukemic efficacy coupled with low toxicity and high degree of compliance. This improved antileukemic efficacy was certainly caused by the modified consolidation therapy. Although it is unclear which part of the reinforced consolidation therapy (ATRA or chemotherapy or both) may have led to the impact observed in the outcome, it is likely that the addition of ATRA has had a significant role. Based on these results and those recently reported by the GIMEMA Group,[7] we believe that the current consensus on the simultaneous administration of ATRA and chemotherapy for induction and maintenance therapy of APL could be extended to the consolidation phase. Based on risk-adapted strategies, future clinical investigations should focus on developing new therapeutic approaches to decrease the relapse rate in high-risk patients with hyperleukocytosis at presentation and progressively decreasing treatment intensity for the remaining patients.

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EMERGING THERAPEUTIC STRATEGIES IN ACUTE PROMYELOCYTIC LEUKEMIA: WILL LESS BE MORE?

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Introduction

Acute promyelocytic leukemia (APL) has emerged as a highly curable subtype of acute myeloid leukemia (AML). With current therapy that includes all-trans retinoic acid (ATRA) and anthracycline-based induction, complete remission (CR) is achieved in approximately 85%-95% of patients.[1-4] The early death rate is approximately 5%-10% and the majority of early deaths are attributable to hemorrhage.[5] Once in CR, patients routinely receive at least two cycles of consolidation with anthracycline-based chemotherapy. Early randomized trials have shown that maintenance therapy with either ATRA, low-dose chemotherapy, which usually includes methotrexate and 6-mercaptopurine, or both, is beneficial.[1,2] With such strategies, the overall survival (OS) at 3-5 years ranges between 70%-95%.[6,7] These outstanding results are unprecedented in the therapy of adults with AML and represent an inspiring example of progress in molecular and clinical investigation. Prognostic factors exist which can identify subsets of patients with a less favorable prognosis who are candidates for novel strategies. Age older than 55-60 years has been shown to present a less favorable outcome than younger patients.[2,8-10] Perhaps the most important prognostic factor is the presenting white blood cell count (WBC) of >10,000/μL. The Spanish Cooperative Group PETHEMA has collaborated with the Italian Cooperative Group GIMEMA and have identified three risks groups depending on the presenting WBC count and platelet count.[3] Patients can be characterized as either low-risk, intermediate-risk or high-risk. Expression of the CD56 antigen has also been suggested to be a poor prognostic factor.[11] The presence of internal tandem duplication mutations in the FLT3 gene may confer a less favorable prognosis.[12,13] The presence of additional cytogenetic abnormalities has not, in general, been shown to adversely affect outcome.[14,15]

Minimizing chemotherapy in APL

Several studies have suggested that chemotherapy may be minimized in some patients with APL. This may be an important goal given the potential for the development of secondary myelodysplastic syndromes, AML and cardiomyopathy in patients treated for APL with increased doses of anthracyclines and maintenance therapy.[16-18] Firstly, a retrospective analysis and a large prospective phase II study carried out by the PETHEMA have suggested that cytarabine may not be required.[3,7,19] However, a recent prospective randomized trial carried out by the European APL Group suggested otherwise.[20] This study randomized patients to daunorubicin, cytarabine, and ATRA or daunorubicin and ATRA alone without cytarabine. The study was discontinued early because of a higher relapse rate of non-cytarabine arm suggesting that cytarabine should not be eliminated. These results stand in contrast to the results of PETHEMA study. Differences between these two studies include the anthracycline used (idarubicin was given in the PETHEMA study and daunorubicin in the European APL group study) and the administration of ATRA in consolidation to many patients in the PETHEMA studies, but not in the European APL group study. Secondly, ATRA has now been administered in consolidation with apparent benefit, perhaps permitting reduction in cytotoxic chemotherapy.[7,21] Thirdly, new effective agents which are not directly cytotoxic may replace conventional chemotherapy (Table 1).

Table 1. Novel agents for APL.

Agents	Rationale
Agents already in clincal trials	
Arsenic trioxide	Induces differentiation and apoptosis
Gemtuzumab Ozogamicin	Effective in relapsed/refractory APL APL cells highly express CD33
	Effective in relapsed refractory APL and in untreated APL
Agents with Potential Activity in APL	
FLT3 inhibitors	FLT3 gene mutations in ~30% of APL patients
Antiangiogenesis agents	Increased blood vessel formation and VEGF production in APL
Alemtuzumab (with ATRA)	ATRA increased expression of CD52 on APL cells
Curcumin	Suppresses NF-Kappaβ in HL-60 cells
	Synergistic with ATRA in HL-60 cells
	Induces differentiation (with ATRA) in NB4 cells and NB4-R1

Arsenic trioxide (ATO) is highly effective as a single agent in relapsed and refractory APL and the combination of ATO and ATRA has been shown to be potentially synergistic.[22,23] Fourthly, the immunoconjugate, gemtuzumab ozogamicin (GO) appears to be quite effective in patients with APL, possibly related to the high expression of the surface antigen CD33.[24-26] Finally, four other strategies deserve further testing. All-trans retinoic acid can induce expression of CD52 suggesting a potential role for the antibody alemtuzumab.[27] Increased angiogenesis and VEGF production in APL raises the possibility that antiangiogenesis agents may be useful.[28] Given the frequency of the FLT3 gene mutations in APL, FLT3 inhibitors should also be studied. Finally, curcumin, a compound isolated from the spice turmeric, suppresses activation of NF-Kappaβ and AP-1 in HL-60 cells is synergistic with ATRA and vitamin D3 in inducing differentiation of HL-60 cells.[29,30] Curcumin also induces differentiation of NB4 cells and resistant APL cells (NB4-R1) when combined with ATRA.[31] Although maintenance has become routine in patients with APL, two studies have suggested that among patients who have achieved molecular CR, maintenance therapy may not be beneficial and can be eliminated.[32-34] The study carried out by GIMEMA group has suggested that neither ATRA, low-dose chemotherapy nor the combination as maintenance improves outcome in patients who are molecularly negative after consolidation.[32] Similarly, the Japanese Acute Leukemia Study Group (JALSG) randomized patients in molecular remission to intensive maintenance chemotherapy alone (without ATRA) or observation and observed no benefit for the maintenance therapy.[33,34] Finally, one small study from the Princes Margaret Hospital suggested that when ATRA is administered during consolidation with an otherwise standard approach of ATRA and anthracycline-based chemotherapy for induction, maintenance might not be necessary.[21] Patients who are at low-risk by presenting with a low WBC as well as those with intermediate-risk have an excellent outcome. Such patients may not benefit from maintenance therapy.

Improving outcome in high-risk patients

Patients with APL classified as high-risk have a less favorable outcome that those with either low-dose or intermedi-

ate-risk when treated with current therapeutic strategies. A number of approaches may improve outcome in such patients. As indicated above, several studies have suggested that cytarabine can be potentially eliminated from induction and consolidation. However, other studies have suggested that in patients with high-risk disease, the administration of high-dose cytarabine may be beneficial.[35,36] The German AML Cooperative Group (GAMLCG) has suggested that when high-dose cytarabine is administered in induction, the presence of a presenting high WBC count does not appear to be a risk factor for relapse. A second study conducted by the GIMEMA has suggested that relapse rate for patients receiving high-dose cytarabine in consolidation is lower than those who did not (29% vs 2% p=0.0004).[37] A second strategy to improve outcome in high-risk patients may be the addition of novel effective agents such as gemtuzumab ozogamicin (GO) which may permit the reduction or possibly the elimination of cytotoxic chemotherapy. Gemtuzumab ozogamicin has been combined with ATRA in previously untreated patients, with idarubicin administered for the development of high WBC count, with a CR of approximately 84% and a molecular CR of 100%.[24] Lo Coco and colleagues administered GO to 16 patients in molecular relapse and all patients achieved a molecular remission.[25] Several strategies exist to incorporate ATO in the treatment of high-risk patients. Arsenic could be combined with ATRA with or without chemotherapy for induction. In addition, arsenic can be administered in consolidation as has been done in the North American Intergroup Study C9710 which recently completed accrual. Finally, arsenic may prove to be useful after consolidation for those small number of patients who remain persistently molecularly positive.

An additional strategy to improve outcome of high-risk patients is high-dose chemotherapy with hematopoietic stem cell transplantation (HSCT). A retrospective study carried out by the European APL Group suggests that autologous HSCT for APL in second CR may be associated with a better outcome than allogeneic HSCT, primarily related to a significantly lower treatment-related mortality rate.[38] The results of autologous HSCT in second CR have been encouraging, particularly if molecularly negative cells can be collected.[39,40] For those patients with evidence of persistent molecular disease in various hematologic remissions, allogeneic HSCT may be an option.[41] Preliminary data from the CIBMTR suggest that HSCT maybe a useful strategy for some patients with APL in first CR at high-risk of relapse.

Treatment of older adults with APL

The treatment of older adults with APL remains a challenge. Historically, such patients have had a less favorable outcome those of younger patients, primarily attributable to treatment-related mortality as well as relapse. Recent studies have suggested that a reduction in the intensity of consolidation of chemotherapy in such patients may be beneficial and lead to a better outcome.[8, 10, 42]

Summary

The excellent outcome of the majority of patients with APL treated with contemporary therapeutic strategies represents a genuine triumph in the field of hematologic malignancies. Such success now affords the opportunity to avoid potential short- and long-term toxicities of conventional cytotoxic chemotherapy. Leukemic promyelocytes are uniquely sensitive to a variety of effective novel agents. Many are being rapidly incorporated into new regimens which will likely permit less cytotoxic chemotherapy. Furthermore, preliminary laboratory studies have evaluated other novel strategies, such as antiangiogenesis or FLT3 gene inhibitors, are encouraging. It seems inevitable that the introduction of combinations of new agents will continue to encourage reduction, or possibly elimination, of cytotoxic chemotherapy in the treatment of many patients with APL.

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