Patients with high-risk acute promyelocytic leukemia need maintenance therapy for 1 year - the PROS

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Acute promyelocytic leukemia (APL) is certainly considered a subtype of acute myeloid leukemia (AML). However, most fundamental features of APL are completely dissimilar from all other subtypes of AML. For example, there is essentially no primary resistance at diagnosis, marrow aplasia following chemotherapy is not required to achieve complete remission (CR),[1] the majority of patients present with leukopenia,[2] there is no period of antecedent myelodysplasia, and patients with APL arising after prior exposure to cytotoxic chemotherapy are as highly curable as those with *de novo* disease.[3] Furthermore, historically, since the demonstration of benefit almost four decades ago, maintenance therapy including low-dose cytotoxic chemotherapy routinely has been administered to all patients with APL, but not to patients with other AML.[2,4] Most remarkable and distinguishing, the majority of patients with APL can be cured with either no chemotherapy or only modest amounts of chemotherapy with treatment based on the combination of all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO). Even among high-risk patients (defined as presenting white blood cell count [WBC] >10x10^9/L) the relapse-free survival (RFS) and apparent cure rate is 90% or higher.[5] Focusing solely on low-risk patients the APL0406 randomized clinical trial demonstrated that the event-free survival (EFS) at 72 months was 96.6% among patients treated with ATRA + ATO induction and consolidation without chemotherapy (except hydroxyurea to control the WBC) compared to 77.4% in the ATRA + chemotherapy group (P=0.0002).[6,7] Relying on the potency of ATO, maintenance was not administered to patients in the ATRA + ATO arm abandoning the historical therapeutic paradigm in APL of induction, consolidation and maintenance. This trial established a new standard of care for low-risk patients. Indeed, the question of the necessity for maintenance in low-risk patients, who represents approximately 75% of newly diagnosed patients, treated with ATRA + ATO definitively has been settled. However, the role of maintenance among high-risk patients remains the subject of debate.

It is useful to consider the developmental history of therapy for APL in two eras: the ATRA (approved by the United States Food and Drug Administration in 1995) era and the ATO (approved in 2000 for relapsed or refractory disease and in 2018 with ATRA for newly diagnosed disease) era. A series of clinical trials, some randomized and conducted by cooperative oncology groups, employing ATRA + anthracycline-based chemotherapy for induction and consolidation before the ATO era showed variable benefits of maintenance. One of the earliest randomized trials to evaluate the role of maintenance in APL was the North American Intergroup I0129 trial.[8] This trial randomized patients to either ATRA or daunorubicin plus cytarabine (DA) for induction. Patients who achieved hematologic CR were administered consolidation with a chemotherapy course identical to induction followed by a course of high-dose cytarabine (HiDAC) plus daunorubicin. Those patients remaining in CR underwent a second randomization to maintenance with either ATRA alone for 1 year or observation. Based on both induction and maintenance randomizations the 5-year disease-free survival (DFS) was 16% for patients randomized to DA and observation, 47% for DA and ATRA, 55% for DA and observation, and 74% for ATRA and ATRA.[9] This study showed the most benefit when ATRA was given in both induction and as maintenance and provided the impetus for continued inclusion of maintenance in subsequent clinical trials and in routine clinical practice. The European APL93 trial published 2 years later generated additional information addressing the role of maintenance.[10] This trial randomized younger patients with WBC <5x10^9/L to either daunorubicin plus concurrent ATRA or daunorubicin following ATRA once hematologic CR had been achieved. Older patients or those with WBC >5x10^9/L were not randomized, but received ATRA + chemotherapy. Patients in CR were given two courses of consolidation chemotherapy with DA and then randomized to one of four maintenance arms: no maintenance, ATRA alone, low-dose chemotherapy with 6-mercaptopurine (6-

MP) plus methotrexate or both ATRA plus the same low-dose chemotherapy. Each maintenance arm was continued for 2 years. The 10-year incidence of relapse was 42.3% among patients randomized to observation, 33% for maintenance with ATRA alone, 23.4% among patients randomized to low-dose chemotherapy and 13.4% for patients randomized to both ATRA plus low-dose chemotherapy (P<0.001).[11] The benefits of maintenance were most evident among those patients with WBC >5x10^9/L which would include high-risk patients. There was a relationship between the duration of maintenance and relapse with more relapses occurring in patients receiving less than 1 year in duration. This trial established the combination of ATRA + low-dose chemotherapy with 6-MP and methotrexate as maintenance for at least 1 year as a standard of care and was widely adopted. Both of these studies defined CR based on hematologic parameters rather than molecular findings raising the possibility that some patients may not have achieved molecular CR before maintenance was given. A dataset derived from two consecutive European trials, APL93 and APL2000, reported the accrual of 204 patients with high-risk disease.[12] The therapy in APL2000 was the same as in APL93 except high-risk patients received increased cytarabine dose in the second consolidation. All high-risk patients were administered combination ATRA plus low-dose chemotherapy for maintenance. In a multivariate analysis maintenance was the strongest prognostic factor for relapse, EFS and overall survival (OS) among patients with WBC 10-50x10^9/L providing further evidence for the benefit of maintenance. Yet not all studies conducted before the introduction of ATO showed the effectiveness of maintenance. The APL97 trial carried out by the Japan Adult Leukemia Study Group (JALSG) randomized patients for induction to three different arms: ATRA alone in patients with WBC <3x10^9/L, ATRA plus idarubicin and cytarabine (IA) if the WBC was 3-10x10^9/L, or ATRA plus IA in an intensified dose and schedule (3 instead of 2 doses of idarubicin and a higher dose of cytarabine) if the WBC was >/=10x10^9/L.[13] Patients in molecular CR were consolidated with three courses of intensive chemotherapy (mitoxantrone and cytarabine, etoposide and D, and IA). Patients still in molecular CR were then randomized to either intensive chemotherapy (referred to as intensified maintenance) for six cycles (DA, and 6-MP; cytarabine and mitoxantrone; cytarabine, etoposide and vindestine; and cytarabine, aclarubicin, and 6-MP; cycles 5 and 6 were identical to the first and third cycles) or observation. The disease-free survival (DFS) at 6 years was 63.1% for patients randomized to maintenance and 79.8% for patients randomized to observation (P=0.2) In fact, the OS at 6 years was 98.8% among patients randomized to observation compared to 86.2% for patients randomized to maintenance (P=0.014) One can argue that since maintenance given in this trial was intensive and limited to six cycles it functioned as additional consolidation and not as maintenance as classically defined (prolonged low-dose, often oral, outpatient chemotherapy). Furthermore, one patient developed apparent therapy-related myelodysplastic syndrome and another developed AML both in the chemotherapy arm. This is a rare occurrence among ATRA + ATO-treated patients. The Gruppo Italiano Malattie Ematologiche dell'Adulto (Italian cooperative group GIMEMA) conducted a trial (0493) in which all patients received induction with ATRA plus idarubicin.[14] Patients in hematologic CR were administered three courses of consolidation with IA, mitoxantrone and etoposide, followed by IA plus 6-thioguanne. Patients in molecular CR were then randomized to the same four arms as in the APL93 trial, but subsequently when ATRA was shown to be beneficial as maintenance the protocol was amended to include only the two ATRA-containing arms. With long follow-up, at 12 years the DFS was not different between the four maintenance groups. Did the substitution of idarubicin, a putatively more potent agent, abrogate potential benefit from maintenance?

Arsenic trioxide is the single most active agent in APL.[15] The introduction of ATO into clinical care completely transformed the therapeutic paradigm. The AML17 trial carried out by the National Cancer Research Institute (NCRI) randomized patients with documented molecularly positive APL to either ATRA + ATO (5 courses) with ATO given at the alternative schedule of daily day (D)1-5 of each course then twice weekly on weeks 2-8 of course 1 and weeks 2-4 of courses 2-5 or ATRA + idarubicin for induction then idarubicin D1-4, then mitoxantrone D1-4 then idarubicin D1 for consolidation.[16] High-risk patients could receive a single dose of gemtuzumab ozogamicin (GO) and 28 of 30 patients were treated as such. No maintenance was given to any patient on either arm. In low-risk patients the EFS at 4 years was 92% in the ATRA + ATO group and 71% in the ATRA + chemotherapy group (P=0.008). However, the difference was not significant in the high-risk patients (87% *vs*. 64%) (P=0.07). OS at 4 years did not differ between the two groups with OS of 95% in the ATRA + ATO group and 90% in the ATRA + chemotherapy group nor among high-risk patients, 87% compared to 84%, respectively (P=0.5) Only one case of therapy-related AML was observed in the ATRA + chemotherapy group. Although there were only 30 high-risk patients, excellent results with multiple courses of ATRA + ATO were achieved without maintenance. North American Intergroup protocol C9710 randomized patients to ATRA + DA followed by two courses of consolidation with ATRA + daunorubicin or the same induction and consolidation + two courses of ATO.[17] Following consolidation patients were randomized to maintenance with either ATRA alone or ATRA + 6-MP and methotrexate for 1 year. Fifty-eight patients had high-risk disease. In this study ATO during consolidation improved EFS among patients with high-risk disease. At the time of publication too few events had occurred to determine the benefits of maintenance.

The APML4 trial conducted by the Australasian Leukemia

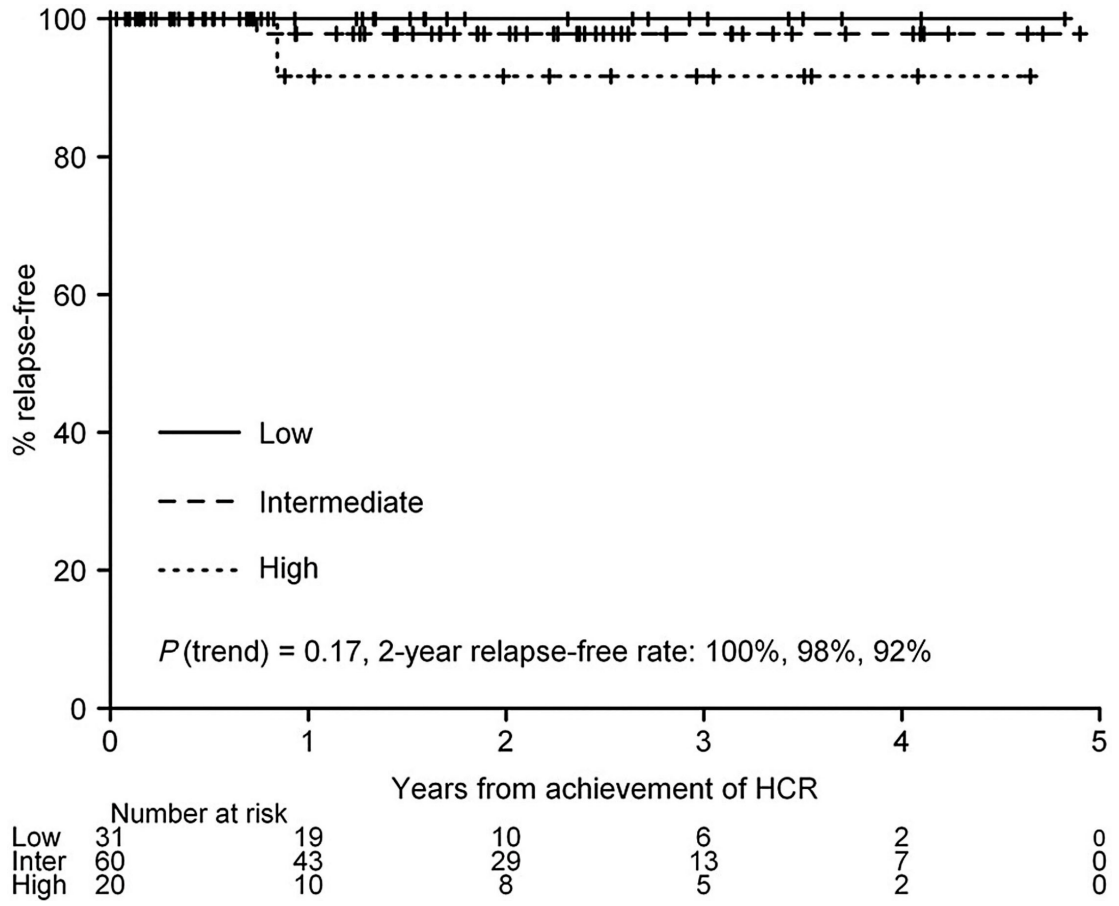

Figure 1. Curve estimated by the Kaplan-Meier product limit estimate. Stratification by Sanz risk category. Figure reproduced, with permission, from Iland HJ, *et al*.[5]

and Lymphoma Group (ALLG) was a phase II trial of ATRA plus idarubicin on D2, 4, 6, 8 followed by ATO starting on D9 all followed by two courses of consolidation with ATRA + ATO. Maintenance with ATRA + 6-MP and methotrexate was continued for 2 years.5 The 2-year failure-free survival (FFS) was 88.1% and OS 93.2%. The relapse-free survival for high-risk patients was 92%, and OS 96.8% (Figure 1). Only one patient developed a second malignancy, a squamous cell carcinoma of the skin which occurred during consolidation and before any exposure to maintenance. This regimen has become popular given its high efficacy particularly in high-risk patients, and its simplicity. However, given the apparent synergism between ATRA and ATO the contribution of maintenance in this trial is not clear. Investigators at the MD Anderson Cancer Center reported a trial similar in some aspects to the design of the APML4 trial, but with important differences.[18] Induction included ATRA + ATO and a single dose of GO instead of idarubicin for high-risk patients or those with low-risk who developed leukocytosis during induction. Patients in CR were given four courses of ATRA + ATO without maintenance. The 5-year EFS, DFS and OS were 85%, 96%, and 88%, respectively, for low-risk patients 87%, 99% and 89%, respectively, and for high-risk patients they were 81%, 89% and 86%, respectively (Figure 2). Eight patients developed a second malignancy and died in CR, but the investigators believe these second malignancies (GIST, prostate, head and neck, melanoma, pancreatic) were attributable to unrelated causes. Five of the 52 high-risk patients relapsed. This regimen builds on the APML4 trial in that it is “chemotherapy-free” except a single dose

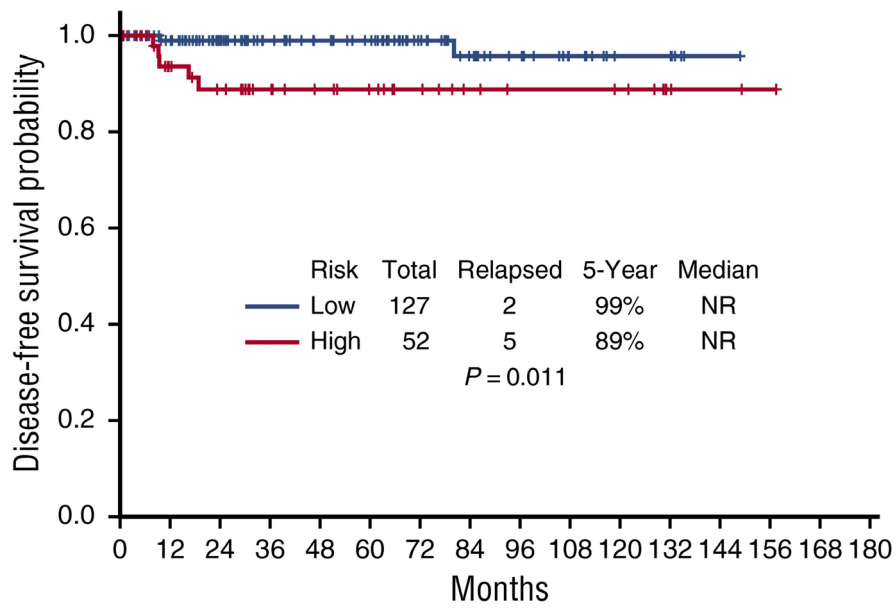

Figure 2. Survival curve using the Kaplan-Meier method. Disease-free survival by risk group. Figure reproduced, with permission, from Abaza Y, *et al*.[18]

of GO and deletes maintenance. Can we hypothesize that the additional two courses of ATRA + ATO consolidation provides the same benefit as 2 years of maintenance? The North American Intergroup trial S0535 treated high-risk patients with ATRA, ATO and one dose of GO for induction. Patients were then consolidated with two courses of ATO, two courses of ATRA + chemotherapy with daunorubicin, and two courses of a single dose of GO followed by 1-year duration of maintenance with ATRA + 6-MP and methotrexate.[19] The 3-year EFS was 78% and OS was 86%. Of the 49 patients who began maintenance seven discontinued

(adverse events or voluntary withdrawal). The APL15 trial from China randomized patients in all risk groups to either ATRA + ATO for induction, consolidation and maintenance or ATRA + ATO with chemotherapy with IA or DA for induction followed by three courses of consolidation with ATRA + ATO and DA or IA, then maintenance with ATRA + ATO for six to ten cycles.[20] The authors suggest that high-risk patients can be treated with only multiple courses of ATRA + ATO once in CR. ATRA + ATO without anthracycline or GO controlled the WBC with hydroxyurea. However, the number of courses of ATRA + ATO to administer as post-remission therapy is not known, but the APML4 and MD Anderson studies suggest less than six to ten.

The European APOLLO trial is among the first randomized trials to accrue only high-risk patients. This trial randomized newly-diagnosed high-risk patients to ATRA + ATO with two doses of idarubicin on D1 and D3 followed by four courses of ATO and ATRA or ATRA + chemotherapy (ATRA + idarubicin induction, then 3 courses of chemotherapy-based consolidation, followed by maintenance).[21] The 2-year EFS was 89% in the ATRA + ATO arm and 72% in the ATRA + chemotherapy arm, respectively (P=0.02). Molecular relapse was observed in zero and six patients in the ATRA + ATO arm and ATRA + chemotherapy arms, respectively. The OS rates at 2-years were 93% and 87%, respectively (P=0.33) (Figure 3). These encouraging results suggested that high-risk patients treated with a limited amount of anthracycline and ATRA + ATO in induction followed by four additional courses of ATRA + ATO may obviate the need for maintenance therapy.

The role of anthracycline or GO in APL in induction may be as much to control the WBC and consequent complications as for its potential antileukemia benefits.

Effective treatment of APL continues to evolve. The almost universal inclusion of ATO where available when combined with ATRA in treatment protocols has permitted the reduction of treatment intensity with the elimination of all chemotherapy including maintenance in low-risk patients and reduction in the dose and schedule of ATO, and suggests the role of maintenance for high-risk patients to be revisited. It is timely to re-examine the role of maintenance with the increasing availability of oral arsenic.[22] ATO and GO are not available in some parts of the world. In addition, there are patients who cannot tolerate ATO. These patients can be treated with ATRA and anthracycline-based chemotherapy for induction and consolidation then 1-2 years of ATRA + 6-MP and methotrexate. High-risk patients for whom ATO

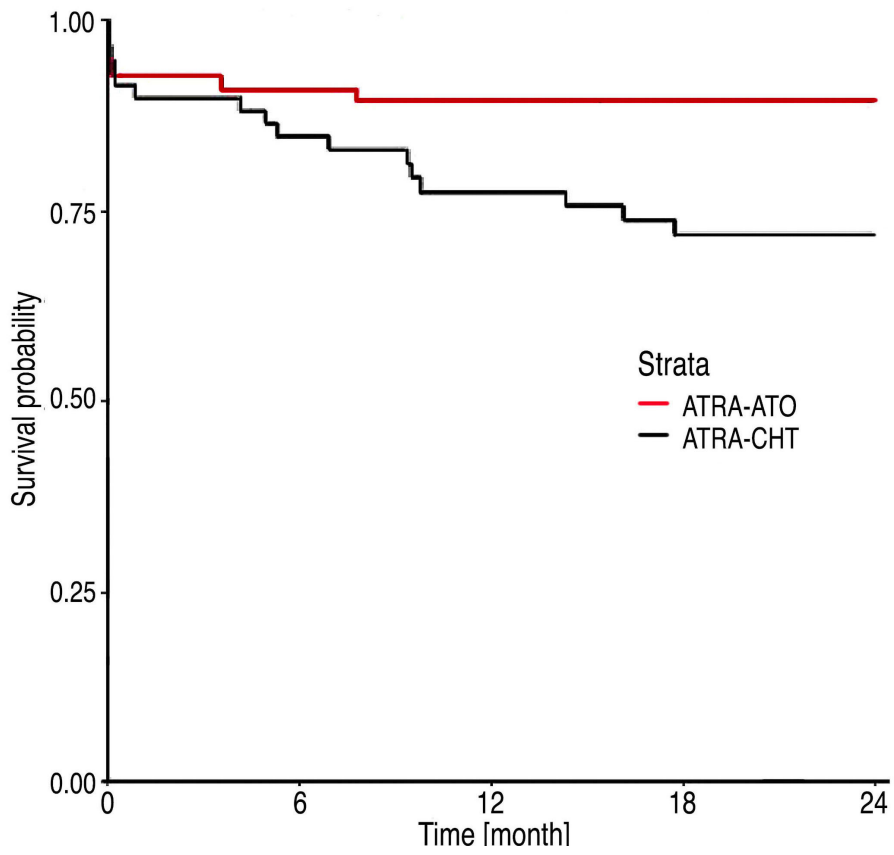

Figure 3. Event-free survival. ATRA-ATO *versus* ATRA-chemotherapy. Figure reproduced, with permission, from Platzbecker U, *et al.*[21]

Table 1. Studies which included high-risk patients with newly diagnosed acute promyelocytic leukemia treated with ATRA/ATO-containing regimens.

Protocol	N	Induction	Consolidation	Maintenance	Outcome
AML17[16]	28	ATRA/ATO, GO x1	ATRA/ATO x4	None	4-yr DFS 89%
APML[5]	24	ATRA/ATO, ida x4	ATRA/ATO x4	ATRA/6MP/MTX	2-yr EFS 92%
C9710[17]	55	ATRA/DA	+/-ATO x2, ATRA daily x7/D x3	ATRA+/-6MP/MTX	3-yr EFS 60%
MD Anderson[18]	54	ATRA/ATO, GO x1	ATRA/ATO x4	None	5-yr DFS 89%
S0535[19]	70	ATRA/ATO, GO x1	ATRA x25 D x2, D x2/ ATRA x7, GO x2	ATRA/6MP/MTX	3-yr EFS 78%
APL15[20]	40	ATRA/ATO	ATRA/ATO, x1	ATRA/ATO x5	2-yr EFS 85%
APOLLO[21]	68	ATRA/ATO, ida x2	ATRA/ATO x4	None	2-yr EFS 89%

ATRA: all-*trans* retinoic acid; ATO: arsenic trioxide; GO: gemtuzumab ozogamicin; DA: daunorubicin and cytarabine; ida: idarubicin; 6MP: 6-mercaptopurine; MTX: methotrexate; DFS: disease-free survival; EFS: event-free survival; x: number of courses, yr: year; D: day.

is available, are best treated according to one of several protocols with proven high efficacy (Table 1). The APML4 protocol which includes 2 years of oral maintenance has become a current standard of care. This regimen is convenient and has the advantage of limiting the number of ATO + ATRA courses to a total of three. The risk of secondary malignancies following completion of the entire treatment protocol is negligible. A potentially important and highly recommended admonition is, when possible, to treat patients in the context of a clinical trial, recommended protocol or guidelines as opposed to routine clinical practice since such an approach may yield better results.[3,23]

Disclosures

The author discloses advisory boards for SDK Therapeutics, Moleculin, Foghorn Therapeutics, HOVON HO156.

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