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

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"Virtue is the golden mean between two vices, the one of excess and the other of deficiency" - Aristotle.

Aristotle's philosophy lies at the center of the conundrum regarding the requirement for maintenance in the management of high-risk acute promyelocytic leukemia (APL). My own perspective is that "enough is enough, provided it's the right stuff."

A debate about the role of maintenance requires some historical context, since the treatment of APL has evolved dramatically over the last 30 years from its original reliance on anthracycline-based chemotherapy.[1] The introduction of all-*trans* retinoic acid (ATRA),[2] which was subsequently shown to target the underlying genetic lesion,[3] was the impetus for a divergence in treatment from that used for other forms of acute myeloid leukemia (AML).

The superiority of ATRA in combination with chemotherapy over chemotherapy alone was convincingly demonstrated by the North American Intergroup I0129 trial[4] and also by the European APL 91 Group,[5,6] and AIDA-like protocols (ATRA and 4 doses of idarubicin in induction followed by 3 cycles of consolidation chemotherapy) emerged as particularly effective.[7,8] Using that approach, the Italian GIMEMA and Spanish PETHEMA cooperative groups showed that the risk of relapse was primarily dependent on the white blood cell (WBC) and platelet counts at initial presentation.[9] In what became known as the Sanz risk classification, high-risk (HR) patients were identified by a WBC count >10x10^9/L, whereas a platelet count below or above 40x10^9/L stratified the remainder into intermediate-risk (IR) and low-risk (LR) subgroups respectively. The term standard-risk (SR) was also used to identify non-HR patients (i.e., IR + LR combined). Although risk category was initially defined in terms of a patient's relapse risk, a WBC count >10x10^9/L at presentation has also proven to be the most consistent determinant of early death (ED) in APL.[10] Therefore the term HR now encompasses patients at increased risk of both ED and relapse, but as the association with ED is not particularly pertinent to the current discussion around maintenance therapy, it will not be addressed further.

The Sanz risk classification provided a framework for the adoption of risk-adapted treatment approaches attempting to reduce relapse rates; the strategies employed included (i) combining ATRA with chemotherapy in consolidation as well as induction, (ii) intensification of chemotherapy for HR patients, and (iii) reduction of chemotherapy for LR patients. Chemotherapy intensification involved additional anthracycline doses and/or additional chemotherapeutic agents, especially intermediate-dose cytarabine. Although successful in reducing the relapse risk for HR patients, the benefit of these protocols was partially offset by excessive deaths in remission (3-5%) involving patients who were potentially already cured.[11-13]

The role of maintenance in ATRA + chemotherapy protocols proved to be highly controversial. As elaborated by Dr Tallman,[14] evidence both for and against its use emerged,[4,15-18] and the value of maintenance became the subject of a Cochrane systematic review.[19] Nine randomized controlled trials were included in the meta-analysis which compared any maintenance *versus* observation, ATRA-based maintenance *versus* non-ATRA-based maintenance, and maintenance with ATRA alone *versus* ATRA with chemotherapy. None of the three comparisons showed a statistically significant difference in overall survival (OS), but improved disease-free survival (DFS) was demonstrated for any maintenance *versus* observation, and for ATRA with chemotherapy over ATRA alone. Unfortunately, despite the inclusion of more than 2,000 patients, there were not enough data to analyze the primary outcomes according to risk stratification, and therefore a particular benefit for maintenance in HR patients could not be demonstrated across all the studies involved. Dr Tallman however correctly highlights the data provided by the European APL group's APL93 protocol, which demonstrated

triple maintenance with ATRA, 6-mercaptopurine (6MP) and methotrexate (MTX) was superior to ATRA monotherapy, 6MP/MTX without ATRA, and no maintenance at all.[15,20] This benefit was indeed more marked in patients with initial WBC counts >5x10^9/L, and therefore encompassed what we regard as HR patients, and a subsequent comparison of HR patients treated with the APL93 protocol and the more chemotherapy-intensive APL2000 protocol reinforced that conclusion.[21] That analysis however is complicated by the fact that these were sequential trials (APL93 accrued from 1993-1996, and APL2000 from 2000-2004) with all the inherent distortions that introduces. The comparison is also influenced by the design of the trials; APL93 included a four-way randomization for maintenance, whereas APL2000 with the more intensive consolidation was restricted to triple maintenance therapy for all patients, and therefore dissecting out the relative contributions of non-randomized chemotherapy intensification and the various components of maintenance therapy is not straightforward. Whether maintenance played any role in reducing relapses in HR patients who also received intensified consolidation chemotherapy is unclear, as triple maintenance was routinely administered by default in the risk-adapted protocols conducted by GIMEMA (AIDA2000),[11] PETHEMA (LPA2005)[12] and the European APL group (APL2000).[13]

With regards to the toxicity of maintenance, the authors of the Cochrane review concluded that the data available for comparison of grade 3/4 adverse events (AE) were insufficient for inclusion in the meta-analysis; however data from some of the individual studies indicated that AE occurred more frequently in patients who received any maintenance *versus* observation, and in patients who received ATRA with chemotherapy compared with ATRA alone. For example, in the comparison of any maintenance with observation in the I0129 trial,[4] ATRA maintenance was associated with 34% grade 3/4 AE *versus* 2.9% in the observation arm, and discontinuation of maintenance due to AE occurred in 14.1%. Similarly, in the North American Leukemia Intergroup Study C9710 trial,[22] ATRA + chemotherapy maintenance was associated with 36% grade 3/4 AE compared with 24% for ATRA alone (P=0.033). Although the toxicity of maintenance is less severe and less frequent than the toxicity associated with intensive chemotherapy, it is worth noting that in the long-term analysis of the APL93 trial there were six septic deaths reported from 246 patients randomized to 6MP/MTX ± ATRA (2.4%), and a further six were hospitalized for febrile neutropenia.[20] Achieving the right balance between maximal efficacy and minimal toxicity is clearly the ultimate goal of anti-leukemic therapy; the overall experience with risk-adapted chemotherapy intensification and triple maintenance can be regarded as an extrapolation of Aristotle's definition of virtue (the golden mean between 2 vices; Figure 1).

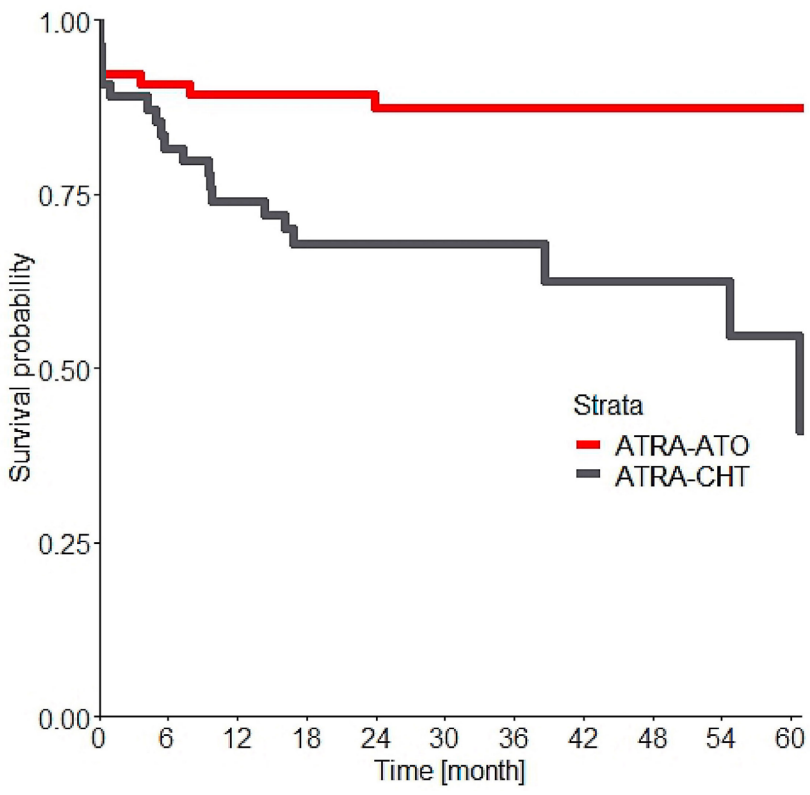
A second divergence of therapy from that traditionally used in AML occurred once the benefit of arsenic trioxide (ATO) was realized,[23-26] underpinned by its ability to target the leukemic stem cells in APL through degradation of the PML::RARα fusion protein.[27-29] Despite the unique toxicity profile associated with arsenicals, including QTc prolongation[30] and neurotoxicity,[31] ATO-based therapy has improved outcomes whilst minimizing the septic complications and long-term cardiotoxicity associated with intensive chemotherapy. For patients with SR disease, a chemotherapy-free approach utilizing ATRA + ATO in induction and consolidation without maintenance has shown clear superiority over ATRA + chemotherapy in induction and consolidation ± maintenance. The approach was ini-

Figure 1. Achieving a balance between increasing therapy to maximize efficacy, and limiting therapy to minimize toxicity. Illustration courtesy of Luk Cox.

tially pioneered by investigators at the MD Anderson,[32] and was subsequently examined in randomized trials conducted by cooperative groups involving GIMEMA-AMLSG-SAL (APL0406)[33,34] and the NCRI (AML17).[35] Although neither arm of the AML17 trial included maintenance, the ATRA + chemotherapy control arm in the APL0406 study based on the AIDA2000 protocol included 2 years of triple maintenance. With a median follow-up of 40.6 months, the chemotherapy-free, maintenance-free ATRA + ATO arm of APL0406 showed statistically significant superiority for OS, event-free survival (EFS), DFS and cumulative incidence of relapse (CIR).[34] With a median follow-up of 67.4 months the AML17 study also showed superiority of ATRA + ATO (using a modified dosing schedule) in SR patients with regards to relapse but not OS.[36] The ATRA + ATO protocols of both APL0406 and AML17 are now widely accepted as standard-of-care for SR APL.[37,38]

Is the advantage of ATO-based therapy in SR patients reflected in improved outcomes for HR patients? Randomized (NCRI AML17) and historically-controlled (ALLG APML4 and COG AAML1331) trials have shown that the combination of ATRA + ATO with gemtuzumab ozogamicin (GO) or limited chemotherapy attenuates or negates the increased relapse risk associated with HR disease,[35,39,40] and the adverse impact of *FLT3* internal tandem duplications noted in several ATRA + chemotherapy studies can also be abrogated.[18,41-45] Even when inclusion of ATO is restricted to consolidation, DFS in HR and SR patients is similar.[22] Data from population-based registries also support the use of ATO-based therapy for both SR and HR disease, as exemplified by the European HARMONY Platform Project[46] which aggregated long-term outcome data from 1,438 patients with both SR and HR APL. In addition to data from the APL0406 and AML17 trials, the HARMONY dataset was sourced from four European national registries (HOVON, AMLSG, Swedish AML Registry, and SAL), representing the largest ever published APL cohort, and demonstrated statistically significant improvements in OS, EFS and CIR that was independent of Sanz risk category. Since oral tetra-arsenic tetrasulfide (delivered as realgar-indigo naturalis formula [RIF]) has been shown to be non-inferior to intravenously administered ATO in both SR and HR disease,[47,48] it is reasonable to assume that ATRA + oral arsenic is also superior to ATRA + chemotherapy. As access to RIF and a liquid formulation of ATO[49] is primarily restricted to mainland China and Hong Kong respectively, the development of alternative oral formulations of ATO[50,51] is eagerly awaited.

Given the undeniable benefit of arsenic-based therapy in HR disease, we must now ask if there is any evidence that maintenance therapy, typically delivered as 1-2 years of intermittent ATRA with 6MP and MTX, is beneficial after arsenic-based induction and consolidation? Unfortunately the randomization to maintenance *versus* observation that was incorporated into ATRA + chemotherapy studies has not been replicated in the ATO era, and studies that specifically address the management of HR disease are scarce. One of the largest was the SWOG 0535 study[52] which included 70 patients with HR disease treated with ATRA + ATO + GO in induction, six cycles of consolidation (2 cycles each of ATO, ATRA + daunorubicin, and GO), and 12 months of triple maintenance with ATRA, 6MP and MTX. The total exposure to ATO was approximately 80 days. The toxicity of consolidation and maintenance was not insubstantial; 60 patients (86%) achieved complete remission (CR) but only 49 completed consolidation and only 38 completed maintenance (54% of the entire cohort). At 3 years, OS was 86%, DFS was 91%, and EFS was 78%, with two deaths in CR. In contrast, a small retrospective analysis from Birmingham of ten patients with HR disease treated



Primary endpoint (2-year event-free survival)			
Therapy	2-year survival	95% CI	*P*
ATRA-ATO	88%	80-96%	0.02
ATRA-CHT	70%	59-83%	

Cumulative incidence of relapse				
Therapy	Incidence of relapse		95% CI	*P*
ATRA-ATO	1.6 %	1/56	0.1-7.5%	0.011
ATRA-CHT	14.0 %	7/42	6.2-26.0%	

Figure 2. Event-free survival and cumulative incidence of relapse in the APOLLO trial stratified by treatment arm. The ATRA-CHT arm includes 24 months of triple maintenance therapy, whereas the ATRA-ATO arm omits maintenance. Presented at EHA2024 Madrid, June 2024,[54] figure courtesy of Dr Platzbecker. ATRA: all-*trans* retinoic acid; CHT: chemotherapy; ATO: arsenic trioxide; CI: confidence interval.

with APML4-like induction (ATRA + ATO + idarubicin) and APL0406-style consolidation (ATRA + ATO) experienced better outcomes despite the omission of maintenance.[53] All patients achieved CR and all were alive in molecular CR at a median follow-up of 38 months; their estimated total ATO exposure was 108 days. A similar study from Beijing (APL14) in 20 HR patients employing ATRA + oral arsenic (RIF) + limited chemotherapy for induction, ATRA + RIF for consolidation and no maintenance also produced impressive results, with 100% complete molecular responses and 89% 3-year EFS.[54] Furthermore, APML4-like induction and APL0406 consolidation without maintenance was employed in the pediatric COG AAML1331 study,[40] and the results were compared with the previous COG AAML0631 protocol. For HR patients, AAML1331 was distinguished from AAML0631 by the addition of ATO and an extra dose of idarubicin in induction, extra ATO without chemotherapy in consolidation, and elimination of maintenance. EFS and OS in AAML1331 were superior (P=0.05 and P=0.02, respectively), whereas maintenance administered in the historical control AAML0631 was associated with 10% febrile neutropenia. These data reinforce the concept that emphasizing reliance on ATO enhances efficacy while avoiding the toxicity of maintenance therapy.

However, the most compelling evidence favouring ATO-based induction and consolidation without maintenance for HR patients was presented in June 2024 at the European Hematology Association.[55] The European Intergroup APOLLO trial for HR APL involved randomization to (i) ATRA + ATO with two doses of idarubicin in induction followed by APL0406-style (ATRA + ATO) consolidation without maintenance, or (ii) the LPA2005 protocol (ATRA + risk-adapted intensified chemotherapy) including 2 years of triple maintenance. With a median follow-up of 31 months, the preliminary results indicate statistically significant benefit for the ATO-based arm without maintenance compared with the comparator ATRA + chemotherapy arm with maintenance (2-year EFS 88% *vs*. 70%; P=0.02 [Figure 2]and CIR 1.6% *vs*. 14.0%; P=0.011). If this striking difference is confirmed at the time of publication the argument that maintenance is required

Table 1. Correlation of arsenic exposure and maintenance duration with outcomes in high-risk patients.

Trial	N of HR patients	Days of arsenic in induction and consolidation*	Duration of maintenance in months	Endpoint assessment in years	EFS in %	Relapses
Group 1: protocols without arsenic that include maintenance						
AIDA2000[11]	129	0	24	6	-	CIR 9%
LPA2005[12]	118	0	24	4	-	CIR 14%
APL2000[56]	74	0	24	7	82	CIR 7%
Group 2: protocols that include both arsenic and maintenance						
C9710[22]	55	50	12	3	66 (estimated)	-
APML4[39]	23	81	24	5	83	CIR 5%
SWOG 0535[52]	70	89*	12	3	78	CIR 7%
AAML0631[40]	35	50	24	3	83	2 relapses
Group 3: protocols that include arsenic without maintenance						
AAML1331[40]	56	113*	0	2	96	CIR 4%
APL14[54]	20	142[#]	0	3	89	2/20 relapses
Birmingham retrospective[53]	10	108*	0	3	-	CIR 0%
AML17[35]	30	113*[§]	0	4	87	1 molecular resistance; 0% relapses
APOLLO[55]	68	110*	0	2	88	1 molecular resistance; CIR 2%

*Number of days of arsenic exposure during induction component estimated from median time to complete remission. [#]The APL14 protocol utilized realgar-indigo naturalis formula (RIF) rather than arsenic trioxide (ATO). [§]Most ATO protocols utilize 0.15 mg/kg/day; in AML17 the ATO was administered at 0.25-0.3 mg/kg on a more intermittent schedule, and therefore the number of days of arsenic is expressed here as 0.15 mg/kg/day equivalents. EFS: event-free survival; CIR: cumulative incidence of relapse; empty cells indicate appropriate data could not be extracted.

for HR disease will be increasingly difficult to justify, just as it is not required in SR disease, provided induction and consolidation are arsenic-based.

Are there any circumstances in which I would recommend maintenance for HR APL? In situations where ATO is unavailable or contraindicated, the risk-adapted ATRA + chemotherapy protocols discussed above[11-13] which include maintenance would be appropriate. Additionally, since it takes 7 months to deliver a full ATRA + ATO consolidation program, proximity to a treatment center that is capable of infusing ATO over a prolonged period of time may be problematic for some patients. In such situations I agree with Dr Tallman that the Australasian Leukaemia and Lymphoma Group APML4 protocol[39] provides a suitable alternative; compared with the APOLLO regimen, it has two extra doses of idarubicin in induction, only two cycles of ATRA + ATO consolidation, and then 2 years of triple maintenance which can be delivered easily in remote settings. This protocol, originally published in 2012, remains recommended by the NCCN[38] for HR APL, but once oral ATO becomes more readily available, I would still favor four cycles of ATRA + oral ATO over two cycles with 2 years of maintenance in virtually all situations. Representative studies showing the correlation of arsenic exposure and maintenance duration with outcomes in HR patients are summarized in Table 1; in general, protocols that provide higher arsenic exposure without maintenance achieve comparable or better outcomes than protocols that include maintenance. In effect, "enough is enough, provided it's the right stuff".

Disclosures

The author has served on an advisory committee for Syros.

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