Acute Promyelocytic Leukemia Can Be Treated Successfully Without Cytotoxic Chemotherapy


In their scholarly article, Dr. Park and Dr. Tallman review the important clinical trials for treating patients with APL reported over the last two decades and argue the case for further reduction and perhaps elimination of conventional cytotoxic chemotherapy in the frontline treatment of this disease.[1]

In their scholarly article, Dr. Park and Dr. Tallman review the important clinical trials for treating patients with APL reported over the last two decades and argue the case for further reduction and perhaps elimination of conventional cytotoxic chemotherapy in the frontline treatment of this disease.[1]

Treatment of APL has evolved during the last several decades following the demonstration that APL cells are sensitive to anthracyclines, the introduction of treatment with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), and the development of highly sensitive techniques such as the qualitative and quantitative polymerase chain reaction (PCR) for diagnosis and for monitoring minimal residual disease.

ATRA and ATO are clearly the two most effective single agents for treatment of APL. Prior to the introduction of ATRA and in the early clinical trials examining the feasibility of single-agent anthracycline therapy of APL, complete response (CR) rates of up to 80% were reported.[2] ATRA monotherapy can produce CR rates of 70%-90%,[3] and in the pivotal North American study of ATO in relapsed APL, a CR rate of 85% was reported.[4] The use of ATRA in frontline therapy for APL and of ATO in relapsed APL is now fully established, and ongoing clinical trials are examining the role of ATO in initial therapy of patients with APL. Studies of single-agent ATO conducted in India and Iran have suggested excellent outcomes, particularly in patients with low-risk disease.[5,6] Mathews and colleagues recently updated the results of single-agent ATO in a cohort of 72 patients with APL and reported probabilities of disease-free survival (DFS) and overall survival (OS) at 5 year post-treatment of 80% and 74%, respectively.[7] In the Iranian study of single-agent ATO, the 5-year DFS and OS were 67% and 64%, respectively.[8] In both studies, the CR rate was about 85%.[7,8] In the latter study, patients who received 4 courses of ATO consolidation had a statistically superior DFS compared with those who received only 1 course of ATO consolidation after achieving CR (P = .03), suggesting benefit from a more protracted course of consolidation.[8]

Although these reports firmly establish ATO as the single most effective drug in the treatment of APL, they also clearly demonstrate that ATO monotherapy is not ideal and combination strategies are needed, particularly in patients with high-risk disease. In the North American Intergroup study reported by Powell and colleagues, the addition of two cycles of ATO in consolidation, after achieving CR with the combination of ATRA and chemotherapy, was associated with a significantly better DFS at 3 years (90% vs 70%, P < .0001), further establishing the importance of ATO in the initial treatment of APL.[9] Although OS at 3 years was better for the ATO-treated patients (86% vs 81%), this did not reach statistical significance (P = .059), likely as a result of the “rescue” of relapsing patients with ATO. The European APL group has also reported the preliminary result of their APL2006 trial, in which patients with high-risk disease were randomized to receive or not receive ATO in addition to chemotherapy consolidation and patients with low-risk APL were randomized to have either ATO or ATRA substituting for cytarabine in consolidation. No statistically different outcomes were reported for any of the treatments compared. Clearly, combining ATO with chemotherapy is feasible, although this may not be the best strategy and the benefits may be diminished by the added toxicity.[10]

Another strategy explored by our group as well as others is to combine ATRA and ATO for the initial induction. This is supported by in vitro studies showing synergy between the two agents.[11] In the studies by the Shanghai group, combination of ATRA and ATO in induction was associated with the greatest degree of reduction of the disease burden (measured by real-time quantitative PCR) at completion of induction, compared with patients treated with ATO or ATRA alone.[12] The 5-year
event-free survival (EFS) and OS were 89% and 92%, respectively, although all patients received combination chemotherapy for consolidation.[13] We have explored the elimination of all chemotherapy in the treatment of patients with APL and have treated patients with newly diagnosed APL with a combination of ATRA and ATO (with gemtuzumab ozogamicin [GO] for patients with high-risk disease—white blood cell count [WBC] > 10 × 10^9/L—and those with a rising WBC after the initiation of therapy).[14] In the most recent update reported at the American Society of Hematology 2010 meeting, 104 patients had been enrolled in the study and the CR rate was 98%.[15] With a median follow-up of 115 weeks, the estimated 5-year event-free survival was 86% and estimated OS was 88%. Only five patients achieving CR had relapsed. It is important to note that strategies that minimize chemotherapy in APL are more plausible and practical due to the availability of an excellent marker of the disease, the PML-RARα fusion transcripts, that can be easily monitored. Prior extensive studies have clearly established that a positive PCR test at the end of induction is inconsequential, but a positive test at the end of consolidation or recurrence of a positive test in a patient who has been persistently negative are highly predictive of relapse requiring intervention with salvage therapy in the form of ATO.[16]

One of the most important ongoing problems in treating patients with APL is the high early mortality and morbidity related to the disease complications at presentation. Recent reports have suggested a higher early death rate and lower OS in patients treated in the community, compared with outcomes reported in clinical trials.[17] This is related to either a selection bias and/or patients presenting with severe hemorrhagic complications that preclude their enrollment in the trials. In another recently reported study, among 100 patients with APL treated at a single institution, 29 were not enrolled into trials; they were more likely to have high-risk disease, and they had a lower CR rate and a significantly lower EFS and OS.[18]

Therefore, treatment of APL begins in the community, with early detection and early initiation of APL-specific therapy (in particular, ATRA) an important remaining obstacle to improving outcome in patients with this disease. Use of more rapid diagnostic techniques, such as immunostaining with anti-PML monoclonal antibodies, may assist in facilitating more prompt institution of treatment with ATRA in the smaller, nonspecialized centers.[19] Future clinical trials in academic institutions and cooperative groups in APL and AML should allow prior therapy with ATRA in order to minimize potential delays in initiation of treatment. ATRA is relatively nontoxic and its initiation in a patient with non-APL leukemia is likely to have minimal consequences.

It is a customary practice in medicine to use the most effective agents in a disease, at their highest tolerable dose until the complete elimination of the disease-propagating factors has been achieved. We and others have demonstrated that by using a protracted course of treatment with ATRA and ATO (with the addition of GO in high-risk patients), and with PCR monitoring, it is very possible to achieve this goal in APL, particularly in patients who are less likely to tolerate the more intensive chemotherapy-based regimens. The introduction of oral arsenicals as well as novel retinoids with potential advantages over ATRA may further facilitate the achievement of this goal by improving the delivery of such a regimen.

Financial Disclosure: Dr. Ravandi has received honoraria and research funding from Cephalon Pharmaceuticals, and has been a member of their speakers bureau.

References:
REFERENCES


Source URL:
Acute Promyelocytic Leukemia Can Be Treated Successfully Without Cytotoxic Chemotherapy

Published on Cancer Network (http://www.cancernetwork.com)

Links:
[2] http://www.cancernetwork.com/oncology-journal
[3] http://www.cancernetwork.com/authors/farhad-ravandi-md