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Chemotherapy-Free Treatment of Acute Promyelocytic Leukemia

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H&O What is acute promyelocytic leukemia (APL)?

FR APL is a subtype of acute myeloid leukemia that traditionally has been well characterized by morphologic, immunophenotypic, and pathologic features such as the presence of granules and multiple Auer rods, which commonly lead to a fairly confident morphologic diagnosis by most pathologists. However, in order to definitively diagnose a patient with APL, patients must have the cytogenetic/molecular pathognomonic characteristic feature, which is translocation between chromosomes 15 and 17, resulting in the fusion gene product *PML-RAR*α. This can be detected by classic cytogenetic analysis, fluorescence in situ hybridization (FISH), or polymerase chain reaction (PCR) and molecular testing for the *PML-RAR*α fusion transcripts.

Historically, APL was one of the most difficult subtypes of acute myeloid leukemia to treat, mainly because of its association with severe disseminated intravascular coagulation and significant coagulopathy leading to a high propensity for bleeding complications.

H&O Could you describe the chemo-free regimen for APL?

FR The introduction of all-trans-retinoic acid (ATRA) in the 1990s was the first big development in treating APL. ATRA induces differentiation in APL cells and reduces the risk of bleeding and coagulation problems. Prior to that, anthracycline-rich chemotherapy was used, because APL cells are very sensitive to anthracyclines and a proportion of patients could be cured.

In the late 1990s to early 2000s, arsenic trioxide was discovered to be an effective agent in the relapse setting and showed very high responses, including complete molecular responses. Later reports showed that arsenic trioxide was the most effective agent in treating APL. In the early part of the 2000s, studies by Estey and colleagues and later by Ravandi and colleagues showed that APL patients can be treated with a combination of ATRA and arsenic trioxide. In the lower-risk patients, this was very effective and was associated with long-term disease-free survival and overall survival. Even in the high-risk patients, the combination ATRA and arsenic plus some additional therapy resulted in high responses and excellent outcomes. This was the initiation of the concept of chemotherapy-free therapy for APL.

Currently, ATRA plus arsenic is typically used for low-risk patients. For high-risk patients, the addition of a third drug has been studied: gemtuzumab ozogamicin, a monoclonal antibody targeted against CD33 and linked to a toxin. Therefore, these regimens completely excluded traditional cytotoxic chemotherapy in induction and consolidation for both low- and high-risk patients.

A randomized study by Lo-Coco and colleagues compared ATRA plus arsenic vs ATRA plus idarubicin with anthracyclines as consolidation treatment in the frontline setting for patients with low-risk APL. Outcomes in both groups were excellent, but this study showed a statistically significant improvement in event-free survival and overall survival for the patients who received ATRA plus arsenic.

H&O Could you describe the regimens for APL that include chemotherapy?

FR The original studies combined ATRA with the traditional chemotherapy for acute myeloid leukemia (cytarabine and anthracyclines), but there was recognition in the 1980s and 1990s that anthracyclines were probably the most potent chemotherapy agents. A number of studies then excluded cytarabine, the most famous using the PETHEMA regimen that combines ATRA with 4 doses of idarubicin and completely excludes cytarabine from the induction regimen.

There are proponents of giving high-dose cytarabine during consolidation in the ATRA plus anthracycline regimens. One potential benefit of this treatment could be reducing the risk of central nervous system relapse, although the risk of central nervous system relapse is extremely low and affects only a small percentage of the total population. The chemotherapy-containing regimens are generally combinations of anthracyclines (typically idarubicin) and ATRA with or without cytarabine.

H&O How do the side effects of the 2 regimens compare?

FR Overall, the chemotherapy-free regimen is better tolerated. Patients have a lower risk of infection and less myelosuppression, nausea, vomiting, and other chemotherapy-related side effects. Chemo-free therapy also does not result in hair loss. This may appear trivial, but I think psychologically, it is an important issue. The only major concern with combining ATRA and arsenic is that both of these drugs are associated with differentiation syndrome; however, studies have not found an increase in the incidence of differentiation syndrome with this regimen. Overall, the chemo-free regimen is better tolerated.

H&O Is chemo-free therapy only beneficial in certain patients?

FR The study by Lo-Coco and colleagues examined low-risk patients only, which account for approximately two-thirds of patients with APL. The effective chemo-free regimen for high-risk patients contains ATRA, arsenic, and gemtuzumab ozogamicin. Unfortunately, gemtuzumab ozogamicin was withdrawn from the United States and European markets and is no longer commercially available. However, patients can receive this drug in ongoing clinical trials. During the American Society of Clinical Oncology (ASCO) 2015 annual meeting, Dr Lancet presented a phase 2 trial of high-risk patients treated with ATRA, arsenic, and gemtuzumab ozogamicin. This study found that the early mortality rate was 11%, which was far better than the expected rate using chemotherapy. This was not a randomized study, but it still shows promising results and long-term follow up is pending.

H&O What are the challenges associated with using chemo-free therapy?

FR One downside is that arsenic trioxide is an intravenous drug given daily for prolonged periods, which can be time consuming. Even during consolidation treatment, patients must come in 5 days a week, 1 month on, 1 month off, for a total of 8 months. However, in our experience at MD Anderson, this has never been a problem because patients know they are reaping the benefits of this therapy.

Arsenic trioxide is associated with prolongation of the QT interval and a risk of cardiac arrhythmia. However, we have not found this to be a concern with appropriate management, which includes avoiding other QT-prolonging drugs, keeping magnesium and potassium levels within the normal ranges, and eating or taking magnesium- and potassium-containing foods or supplements. I cannot recall a single case of a life-threatening arrhythmia in patients we have treated, but in the community setting I would still highly recommend monitoring via electrocardiogram (EKG) on a weekly basis when the patient is being treated.

H&O How widely is chemo-free therapy being used for APL?

FR Chemo-free therapy is now included in the National Comprehensive Cancer Network (NCCN) guidelines, and I believe the use is gradually increasing. At our center, we have been using this for the last 12 years. Patients typically receive the induction treatment at our center and consolidation treatment from the local community physicians. A decade ago, these physicians were concerned about using arsenic trioxide, but with increased use, they have become more comfortable with it.

H&O Is chemo-free therapy being tested in other malignancies?

FR Many targeted agents are being developed in various hematologic malignancies and even solid tumors. For example, chronic myeloid leukemia is now a chemo-free disease, and only oral tyrosine kinase inhibitors are used. I personally think APL is a poster child for cancer therapy, in which we have highly effective, relatively nontoxic, targeted agents and have a good way of monitoring the disease. If this can be achieved for other malignancies, targeted agents can reduce or eliminate the need for cytotoxics. However, this may be a long way away.

H&O Is there anything else that you would like to add or emphasize?

FR It is very important to remember that APL, even low-risk APL, remains a life-threatening condition. No patient should get initial therapy outside of the hospital. All patients should be hospitalized initially because they need aggressive correction of coagulopathy with blood product support, including platelets, fresh frozen plasma, and cryoprecipitate. They also need close monitoring for infections, fluid imbalance, and complications such as differentiation syndrome. We do not discharge patients, even if they are doing well, until approximately 2 weeks into therapy when the risk of differentiation syndrome is subsiding.

Death in APL still occurs; many of the published clinical trials are reporting long-term survival at 85% and 90%, but data from the Surveillance, Epidemiology, and End Result (SEER) Program show that the 3-year survival rate in the community is only approximately 70%. The main reason for this disparity is a delay in diagnosis and initiation of therapy in the community and early death before patients are enrolled in the clinical trials. Patients present to a local primary physician with fatigue or bruising, and sometimes it may take several weeks to correctly diagnose the patient. By the time the patients arrive at the hospital, they can have major complications such as massive intracranial bleeding. Therefore, it is absolutely imperative that any patient with low blood counts, bleeding or bruising problem, or suspicions of APL be referred to a major center immediately. If the physician suspects that the patient has APL, ATRA therapy can be initiated without making a diagnosis. There is a very low risk associated with receiving a few days of therapy with ATRA if the patient does not end up having APL, but a delay in diagnosis and treatment can be catastrophic, even in a young patient. This is a disease that should be 100% curable.

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