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Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Updates on the Treatment of Acute Promyelocytic Leukemia

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H&O What is the standard of care for acute promyelocytic leukemia (APL), and what do we know of response and cure rates?

MT Today, the standard of care for the treatment of patients with APL is all-trans-retinoic acid (ATRA) plus an anthracycline-based chemotherapy program—either daunorubicin or idarubicin and Ara-C. With these strategies, the cure rate in general is approximately 85%. This cure rate is at least double, if not more, than that for patients with other subtypes of acute myeloid leukemia (AML) who achieve complete remission. APL is the most curable of all acute leukemias in adults.

H&O What are the biologic and clinical features that distinguish APL from other subtypes of AML? How do the differences relate to treatment sensitivity?

MT APL is a distinct subtype of AML that is characterized by the accumulation of myeloid cells that appear to be blocked at the promyelocytic stage of differentiation in the bone marrow and the peripheral blood.

I do not think we know the answer to why patients with APL are particularly sensitive to anthracycline. Although the reasons are not completely known, there is a suggestion that the expression of the multidrug resistance inhibitor P-glycoprotein, which serves to extrude chemotherapy from the internal part of the cell, seems to be lowest in patients with APL. Therefore, the anthracycline may be able to enter the cell better than it can in other subtypes of AML. Another suggested possibility is that targeted therapy seems to be directed at a specific molecular abnormality in APL that does not exist in other subtypes of AML. ATRA is a vitamin-A derivative directed at a specific molecular abnormality: the PML-RAR (alpha) fusion transcript. In addition, the leukemic cells appear to be unusually sensitive to anthracycline, perhaps, although not proven, because of low expressions of P-glycoprotein.

In the laboratory, many investigators are trying to identify why APL cells are so sensitive to anthracycline, but we have yet to find a definite explanation.

H&O What are the challenges in APL therapy?

MT One of the most important challenges in APL therapy is to reduce induction mortality. The induction mortality rate that is reported in clinical trials is approximately 10%, but these data include only patients who have survived long enough to participate in a clinical trial. There are a number of patients who do not survive long enough to be registered in a clinical trial, so I think that the actual mortality rate is higher than the 10% that is currently reported. There is some evidence that it may be in the order of 25–30%, which is higher than that of other subtypes of AML.

The reason for this higher induction mortality rate in patients with APL is because of a peculiar bleeding abnormality; patients with APL have a coagulopathy that is unique to this subtype of AML. The leukemic promy-

elocytes release substances that activate the coagulation cascade, affecting both the prothrombotic and profibrinolytic parts of the coagulation system. Patients also have a predisposition towards clotting, but generally, they particularly have a major problem at diagnosis with bleeding.

H&O What are the steps to treat or prevent this bleeding?

MT The first and most important steps are early diagnosis and early institution of therapy, even before the diagnosis is definitively established. The 2 steps that are most important in the initial approach of a patient with APL are the following:

1. Start ATRA at the very first suspicion of the disease, even before the diagnosis is definitively established by cytogenetic or molecular genetic studies.
2. Employ very aggressive blood product support with cryoprecipitate to maintain the fibrinogen and platelet count, even administering blood products 2–4 times a day to maintain a fibrinogen count over 150 mg per cent and a platelet count over 30,000–50,000 /μL for the first few days.

H&O What are the signs and symptoms that a physician should look for, when this disease is suspected?

MT The typical clinical picture of an APL patient is a young individual who often presents with leukopenia, but has a significant coagulopathy and circulating blasts and may have bleeding and bruising. When these signs and symptoms are present, physicians raise the question of AML; any time the question of AML is raised, physicians should consider the possibility of APL. Being aware of the possibility of APL is very important because 1) the treatment is different than all other subtypes, 2) the treatment is highly effective, and 3) the delay in diagnosis or in the institution of therapy while waiting for confirmation of diagnosis can be life-threatening.

H&O Are there any prognostic factors that can predict relapse or early death?

MT Age and white blood cell count are important prognostic factors. Older age, greater than 55–60 years, confers a less favorable prognosis with regard to early death rate; white blood cell count over 10,000 can identify a group of patients in whom the risk of relapse is higher. Many investigators are studying to see if they can identify other prognostic factors that will predict for both early death and relapse.

The presence of chromosome cytogenetic abnormalities in addition to the standard t(15;17) does not seem to confer a less favorable prognosis.

H&O How does age and white blood cell count affect treatment selection?

MT Treatment strategies for patients up to 75–80 years of age are essentially the same. There has been some suggestion that patients older than this may benefit from less consolidation chemotherapy.

There are several strategies a physician can adopt in the case of a patient who has a high white blood cell count at diagnosis or who develops a high white blood cell count in the course of therapy: 1) consider administering high-dose or intermediate-dose cytarabine, depending on the age, in consolidation, or 2) consider administering arsenic trioxide as an early consolidation therapy. Either option appears useful in decreasing the relapse rate in this patient population.

H&O Are there any new agents that are being investigated that can possibly replace or minimize chemotherapy?

MT Tamibarotene (CytRx) is a novel retinoid that is being studied in place of ATRA and may be better than ATRA. It is currently approved in Japan for the treatment of recurrent APL. Preliminary studies done in the laboratory have shown that tamibarotene may be more potent than ATRA. In vitro, it seems to be approximately 10 times more potent than ATRA at causing APL cells to differentiate and die, with a lower affinity for cellular retinoic acid binding protein, which may allow for sustained plasma levels during administration. An ongoing phase II clinical trial (STAR-1) will evaluate the efficacy and safety of tamibarotene as a third-line treatment for APL.

Also, arsenic, although not necessarily new anymore, is very effective in patients with relapsed disease, and it appears effective as an early consolidation therapy. There are some preliminary studies that suggest that it is very effective as an initial therapy particularly when combined with ATRA. Additional studies evaluating the combination of ATRA plus arsenic trioxide are ongoing.

I think these randomized trials that are comparing ATRA plus arsenic to standard chemotherapy as initial therapy will be very important, as will be the further identification of novel retinoids, such as tamibarotene. Fortunately, the outcome for almost all patients with APL is so favorable now that most patients are cured of their disease, an achievement unprecedented in the treatment of adults with AML.