ManagingAML

Therapy-related AML: Its relationship to de novo AML and how it impacts prognosis and treatment

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Welcome to *Managing AML*. I am Dr. Jeff Lancet from the Moffitt Cancer Center in Tampa, Florida. We are talking today about therapy-related AML and how it relates to de novo AML, and how it may impact prognosis and treatment decisions. The common theme of therapy-related AML is that it is a very complex and diverse disease process that is not entirely understood. We define therapy-related AML as AML that arises following prior exposure to cytotoxic chemotherapy, generally speaking, for other cancers.

Therapy-related AML can arise at various timepoints following previous cytotoxic chemotherapy. In some instances, it can occur two to three years following chemotherapy. This often occurs in the setting of prior treatment with a topoisomerase II inhibitor as is often seen in patients with, for example, breast cancer. These types of therapy-related AML are often associated with translocations involving the MLL gene. These types of leukemia are oftentimes responsive to initial induction chemotherapy but are associated with a very poor long-term prognosis.

Then you also have a type of therapy-related AML that is associated with prior alkylating agent exposure. These types of therapy-related AML are often associated with the presence of karyotypic abnormalities such as deletion 5, deletion 7, or a complex karyotype (frequently p53 mutations); these therapy-related AMLs tend to occur after a longer period of latency, often 5 to 10 years following the prior chemotherapy. You can see that there is some diversity in therapy-related AML – both in terms of the clinical presentation and the molecular features – but overall, therapy-related AML is a disease associated with a very poor prognosis and one in which we really struggle every day to properly and appropriately treat, because the treatment options are so limited.

There is also emerging evidence that therapy-related AML may relate to preexisting clones, if you will, that predated even the initial administration of the chemotherapy for another cancer. This has been demonstrated in the setting of p53 mutations which could be unmasked and allowed to propagate in a favorable environment after chemotherapy; this is something that we see not infrequently in the setting of therapy-related AML and is associated with very poor outcomes. The presence of preexisting clonal hematopoietic abnormalities such as p53 and others is an emerging area and one that we need to focus on in terms of trying to identify such patients ahead of time, and possibly employing preventive strategies to reduce the risk of subsequent development of therapy-related AML down the road.

But once it develops, we have to think about how to treat this disease. To date, the therapeutic options are very limited. We typically think about utilizing hypomethylating agent therapy for these patients. In some circumstances, for younger fit patients, intensive induction chemotherapy may be an option. All of these types of therapies should be followed by an allogeneic hematopoietic cell transplant in the future as a way to potentially cure the disease, given the fact that we do not have curative options outside of the transplant arena. We do have the knowledge now that patients with therapy-related AML may benefit from the recently approved drug CPX-351, which is a liposomal formulation of cytarabine and daunorubicin. The phase 3 trial that was recently performed demonstrated an overall survival advantage attributable to CPX-351 compared to 7+3 for patients who had therapy-related AML, so this is a new option for such patients who are fit and considered suitable for more intensive therapy and potentially allogeneic transplant down the line.

Thank you very much for viewing this activity.