Precision medicine in AML in the era of novel agents

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For decades, acute myeloid leukemia (AML) has lagged behind other hematological malignancies with respect to improvements in treatments and outcomes. The majority of AML patients relapse and die from their disease despite initial remission, and long-term survival for older patients is rare. During the last few years, increased understanding of the pathobiology of AML has led to refinements in prognostic models, as well as the developed of targeted therapies. The application of next-generation sequencing (NGS) technologies to identify somatic mutations is now part of the standard of care for both newly diagnosed and relapsed AML patients. The presence of several mutations has been incorporated, along with cytogenetics, into the European LeukemiaNet and other prognostic scoring systems for AML. Also, targeted inhibitors of FLT3 (midostaurin, gilteritinib), IDH1 (ivosidenib) and IDH2 (enasidenib) have become commercially available in the United States and are pending approval in other parts of the world. The term “precision medicine” has been increasingly applied in AML as risk-adapted and biology-adapted treatments have evolved. In addition to molecularly targeted approaches, other subgroups of AML patients have been identified, including those with secondary AML, who may benefit from a liposomal combination of cytarabine and daunorubicin (CPX-351), and those with core-binding factor AML, who may benefit from the addition of the calicheamicin-conjugated CD33 antibody gemtuzumab ozogamicin to standard chemotherapy. Finally, the addition of the BLC-2 inhibitor venetoclax to hypomethylating agents or low-dose cytarabine has emerged as the new standard of care for older patients with AML. Early data suggest that venetoclax combinations have significant activity across molecular and cytogenetic subgroups of patients, but more data are needed to optimize its use. Improved techniques of NGS and flow cytometry have resulted in rapid evolution of the field of measurable residual disease (MRD) in AML. MRD-negative complete remission is the goal of AML therapy and significant work is underway to determine which of the novel agents and combinations will result in the highest rates of MRD negativity. A major challenge for the next few years will be to determine a) how to best “mix and match” the agents described above, as well as other emerging novel agents, and b) how to select which AML patients should undergo allogeneic stem cell transplantation in the era of novel therapeutics.