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LIÇÃO VALADAS PRETO

CAN WE CURE ACUTE MYELOID LEUKAEMIA? HOW?
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There is recent enthusiasm over progress in treating acute myeloid leukaemia (AML). After a 40-year hiatus since cytarabine and daunorubicin were approved there are 5 new anti-AML drugs approvals: (1) gemtuzumab ozogamicin (anti-CD33 monoclonal antibody); (2) midostaurin (*FLT3*-inhibitor); (3) CPX-351 (liposomal cytarabine/daunorubicin); (4) enasitenib (*IDH2*-inhibitor); and (5) ivosidenib (*IDH1*-inhibitor).

This raises the question of whether we can cure AML and how? 1st, we need to recognize AML is a cancer of older persons with a median age of 65-70 years. A healthy 70 year-old male has an estimated additional life expectancy of only 14 more years. Moreover, many 70-year-olds have co-morbidities such as arterio-sclerotic cardio-vascular disease, hypertension, diabetes and kidney disease and some are frail. He also has a 1.5 percent chance of developing a solid cancer every subsequent year.

Consequently, it is not surprising 50 percent of persons with AML >65 years in the US are never treated. Some of these persons should not be treated but others should. There are convincing data of improved survival of persons with AML <60-65 years because of intensive chemotherapy and allogeneic haematopoietic cell transplants. However, there is little progress in treating persons >60-65 years, 5-year survival is now estimated at 27 percent up 4-fold since 1976 when it was 7 percent. However, 5-year survival of persons >65 years is only 5 percent. In studies from the German AML study group we showed more intensive therapy is unlikely to improve survival of older persons with AML.

Consequently, new approaches are needed. Examples include azacitidine and targeted therapies like midostaurin, enasitenib and ivosidenib. Another question is what should be the therapy objective in persons >65-70 years: cure, improved survival or improved *quality-of-life*? In persons <65 years the direction is towards greater individualized therapy, so-called *precision oncology*. For example, persons with a *FLT3*-mutation benefit only slightly from adding midostaurin to cytarabine and daunorubicin. However, more potent *FLT3*-inhibitors are on the horizon such as gilteritinib. Similarly, persons with therapy-linked AML may benefit slightly from CPX-351.

Persons with *IDH1* and *IDH2* mutations may respond to ivosidenib or enasitenib. The sum of these considerations is we may be able to increase the proportion of persons cured of AML and/or increase their survival. However, it is unlikely we will be able to improve survival or cure >50 percent of persons with AML despite substantial progress in our understanding of this cancer.