Best Practice & Research Clinical Haematology 32 (2019) 115

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/issn/15216926

Preface

AML: The future is now or was it yesterday?

We have made great scientific progress in many fields of science, with breakthroughs in medical science leading the way. The last decade has been one of major advances in oncology, including solid tumors and hematologic malignancies. More specifically in the last two years we have seen 8 new drugs approved by the United States Food and Drug Administration (US FDA) for the treatment of AML including 4 targeted therapies (enasidenib and ivosidenib for IDH mutated AML; midostaurin and gilteritinib for FLT3-mutated patients), immune therapies (gemtuzumab ozogamicin for CD33 $^{+}$ AML), novel cytotoxic formulation (vyxeos, liposomal formulation of anthracycline and cytarabine with specific survival benefit in patients with secondary and MDS related AML), BCL2 inhibitor (venetoclax, which in combination with hypomethylating agents azacitidine or decitabine has shown dramatic improvements in outcomes in older AML), and hedgehog pathway inhibitors (glasdegib, which showed a survival improvement when combined with low-dose cytarabine in older AML). To put these breakthroughs in perspective one has to realize that in the prior 4 decades we had only one drug US FDA Approved, gemtuzumab ozogamicin, and this was subsequently withdrawn from the market in 2010 due to non-compelling results in a subsequent confirmatory phase III study. These FDA approvals are the tip of the iceberg and the culmination of decades of successful preclinical and correlative analysis on patients with AML that have helped elucidate the complex molecular and immune architecture of AML, the prognostic impact of various mutations and mutational clusters, and the mechanisms of resistance to traditional cytotoxic and newer molecular and immune targeted therapies. Although it may sound audacious we believe this is only the beginning of the research and a number of exciting therapies including potent and selective FLT3 inhibitors (quizartinib), MDM2-inhibitors, E-selectin inhibitors, bispecific antibodies, immune checkpoint inhibitors, CART cells, and an array of epigenetic modulators are moving forward in clinical development with a number of these already in phase 3 development or with recently completed phase 3 studies. Maintenance is making a resurgence, most convincingly in FLT3-mutated patients post-transplant but also in non transplanted patients with azacitidine based therapies. To top this all a number of the novel agents are entering doublet, and triplet combinations, and we daresay rationally designed concomitant or sequential quadruplets may not be too far away (is anybody thinking this sounds very much like multiple myeloma clinical development di in 2005: if so, indeed it does). With this pace of research and clinical trial activation, keeping abreast of the emerging data with AML is becoming more of a challenge than ever before. It is with this in mind that we have put together this special issue that focuses on novel therapies and research advances in AML: from targeted and immune therapies to BCL-2 inhibition and how we believe these will shape the future of AML therapy to a comprehensive overview of MRD-assessment, emerging modalities for MRD measurement and the clinical impact of MRD. We have also included “hot emerging topics” such as hereditary leukemia's and emerging knowledge regarding CHIP. We have been very fortunate to be able to invite and receive exceptional manuscripts from world leaders in these fields and believe this will be a useful compilation for all those interested in the today and the tomorrow of AML.

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https://doi.org/10.1016/j.beha.2019.05.009
Received 23 May 2019; Accepted 23 May 2019
1521-6926/