Molecular Diagnostics Moving Hematological Malignancies into the Era Of Precision Medicine

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Examples of the molecular and genetic markers in patients with HMs include: (1) MDS: SF3B1, TET2, RUNX1, ASXL1, SRSF2, TP53, IDH1/2, EZH2 and NRAS; (2) APL: PML-RARA; (3) other AML subtypes: RUNX1, NPM1, CEBPA, FLT3-ITD, IDH1/2, DNMT3A, TET2 and BCR-ABL1; (4) ALL: BCR-ABL1, BCR-ABL1-like, ETV6-RUNX1, IKZF1, CDKN2A/B and NOTCH1; (5) CML: BCR-ABL1; (6) Philadelphia chromosome negative chronic myeloproliferative neoplasms (CMPNs): JAK2, CAL-R, MPL, SETBP1, ASXL1 and CSF3R; (7) chronic lymphocytic leukemia (CLL): TP53, NOTCH1, SF3B1, ATM and BIRC3; (8) B-cell lymphomas: MYC, BCL2, BCL6, CCND1/2 and SOX11 expression; (9) T-cell lymphomas: ALK, DUSP22, IKG4 and TP63; (10) Hodgkin's lymphoma (HL): SOC1, STAT6, PD-L1, PD-L2, JAK2, XPO1, JUNB, GNA13, IKBA, REL6, BCL3, BCL6, NFKBIA, NFKBIE, MAFA, MAP3K14, MDM2 and TNFIP3; (11) Hairy cell leukemia (HCL): BrafV600E; and (12) MM: TP53, CCND1, CCND2, CCND3, KRAS, NRAS, BRAF, MAFA, FAM46C

Cancer is a genomic disorder resulting from cellular accumulation of genetic alterations [1]. The first complete cancer genome, obtained from a patient with acute myeloid leukemia (AML), was reported in the year 2008 [2]. Hematopoiesis requires self-renewal and well-organized process of differentiation of hematopoietic stem cells (HSCs) in order to maintain the life-long regeneration of various types of blood cells [3]. Perturbations of normal differentiation of HSCs can result in the 3 main types of hematologic malignancies (HMs): leukemia, lymphoma and myeloma myeloma (MM) [3]. HMs has a molecular genetic basis as they evolve as a consequence of the expression of aberrant genes and/or an aberrant expression of normal genes [4]. The discovery of several novel somatic mutations by next generation sequencing (NGS) has led to the discovery of previously unrecognized genes and molecular pathways that are valuable both diagnostically and therapeutically [5]. The genetic and genomic alterations play a pivotal role in: the diagnosis, disease classification, prognosis and treatment selection in most HMs [1,6,7]. The various cytogenetic techniques, particularly molecular tests, performed in patients with HMs are useful in: provision of insights into the disease biology, establishment of the diagnosis, prognostication, selection of the most appropriate therapy and monitoring response to novel therapies [4,6].

In comparison with Sanger sequencing, that first emerged in 1977 and dominated the field for 3 decades, the new sequencing technologies including NGS have a number of advantages including: higher levels of precision and intensity, higher resolution and shorter time to obtain results [2,8,9]. NGS has revolutionized research in patients with HMs and has recently led to a number of significant discoveries related to: early disease diagnosis, risk stratification, clonal evolution and selection of the most favorable and personalized therapeutic intervention [5].

The majority of genetically-defined leukemias, such as AML, are accurately predictable by gene expression profiling [10]. Treatment-specific sensitivity assays are being developed for targeted therapies such as farnesyl transferase inhibitors in AML and imatinib in BCR-ABL positive acute lymphoblastic leukemia (ALL) [10]. Myelodysplastic syndrome (MDS), AML and ALL are heavily influenced by epigenetics [11-13]. Epigenetic targeted therapies might be particularly appealing as a prolonged treatment in the post-remission setting where they could target specific sub clones once disease debulking has been achieved by the standard cytotoxic chemotherapy administered to induce remission of acute leukemia [13]. Targeted therapies have already revolutionized treatment outcomes in several HMs, particularly: chronic myeloid leukemia (CML), acute promyelocytic leukemia (APL), multiple myeloma (MM) and diffuse large B-cell lymphoma (DLBCL) [11,14,15].

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and DIS3 [5,10,12,13,16-28]. Examples of the novel and targeted therapies that are currently used in the treatment of various HMs include: (1) MDS: lenalidomide, azacitidine and decitabine (2) APL: all trans-retinoic acid and arsenic trioxide (3) other AML subtypes: gemtuzumab, lintuzumab, sorafinib, midostaurin, lestaurtinib and Dr383-IL3 (4) ALL: rituximab, nelarabine, tyrosine kinase inhibitors, blinatumoma and CAR T-cells; (5) CML: imatinib, dasatinib, nilotinib and ponatinib; (6) CMPNs: ruxolitinib (7) CLL: rituximab, ibrutinib, idelalisib, obintuzumab, venetoclax and duvulisib; (8) B-cell lymphomas: rituximab and CAR T-cells; (9) T-cell lymphomas: nelarabine and alemtuzumab; (10) HL: brentuximab vedotin, rituximab, everolimus and nivolumab; (11) HCL: vemurafenib; and (12) MM: lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumomab and isatuximab [12-15,23,29-37].

Precision or personalized medicine refers to the use of the specific characteristics of an individual patient, based on his/her molecular and genetic profiles, to tailor therapies during all stages of care accordingly [38,40,41]. Simply it rejects reliance on the old therapeutic approach "one size fits all" and implies that: (1) provision of the right patient with the right drug at the right dose at the right time, and that (2) optimizing treatment given to an individual patient and maximizing benefit while limiting toxicity [38,39,41]. The use of genetic information; obtained by advanced technology namely molecular genetics, DNA sequencing as well as genomic and epigenetic assays; plays a major role in the design of personalized medicine [38,40,41]. Hematology has been the vanguard of precision medicine. Examples of precision medicine in hematology include: (1) typing of blood group antigens to guide blood transfusion, (2) human leukocyte antigen typing to guide donor selection in solid organ and HSC transplantation, and (3) the use of targeted therapies in patients with BCR-ABL and PML-RARA translocations [14,41].

In conclusion: the recent utilization of many targeted therapies in the treatment of patients with HMs has translated into improved outcomes. The driving force behind these successes and achievements is the introduction of advanced technical techniques in molecular laboratories.

Conflict of Interest
None.

References


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