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Molecular Diagnostics Moving Hematological Malignancies into the Era 0f Precision Medicine

Khalid Ahmed Al-Anazi*

Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, Saudi Arabia

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Corresponding author:
Khalid Ahmed Al-Anazi

kaa_alanazi@yahoo.com

Consultant Hemato-Oncologist and Chairman, Department of Hematology and Hematopoietic Stem Cell Transplantation, Oncology Center, King Fahad Specialist Hospital, Saudi Arabia.

Tel: +966-03-8431111

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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].

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, IKFZ1, 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, IRF4 and TP63; (10) Hodgkin's lymphoma (HL): SOC1, STAT6, PD-L1, PD-L2, JAK2, XPO1, JUNB, GNA13, IKBA, REL6, BCL3, BCL6, NFKBIA, NFKBIE, MAFB, MAP3K14, MDM2 and TNFIP3; (11) Hairy cell leukemia (HCL): BRAFV600E; and (12) MM: TP53, CCND1, CCND2, CCND3, KRAS, NRAS, BRAF, MAF, FAM46C

and DI53 [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, lestuartinib 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 duvilisib; (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]. 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

1 Surrey LF, Luo M, Chang F, Li MM (2016) The genomic era of clinical oncology: Integrated genomic analysis for precision cancer care. Cytogenet Genome Res 150: 162-175.

2 Merker JD, Valouev A, Gotlib J (2012) Next-generation sequencing in hematologic malignancies: what will be the dividends? Ther Adv Hematol 3: 333-339.

3 Hu D, Shilatifard A (2016) Epigenetics of hematopoiesis and hematological malignancies. Genes Dev 30: 2021-2041.

4 Bagg A (1995) The molecular genetics of hematologic malignancies. Clin Diagn Lab Immunol 2: 255-262.

5 Braggio E, Egan JB, Fonseca R, Stewart AK (2013) Lessons from next-generation sequencing analysis in hematological malignancies. Blood Cancer J. 3: e127.

6 Prakash G, Kaur A, Malhotra P, Khadwal A, Sharma P, et al (2016) Current role of genetics in hematologic malignancies. Indian J Hematol Blood Transfus. 32: 18-31.

7 Wan TK (2009-2010) Molecular cytogenetics: techniques, developments and applications. J Hong Kong Inst Med Lab Sci 12.

8 Kulski JK (2016) Next generation sequencing-an overview of the history, tools and "omic" applications. In: Next generation sequencing - advances, applications and challenges. Edited by: Kulski JK. In Tech.

9 Serrati S, De Summa S, Pilato B, Petriella D, Lacalamita R, et al. (2016) Next-generation sequencing: advances and applications in cancer diagnosis. Onco Targets Ther 9: 7355-7365.

10 Bacher U, Kohlmann A, Haferlach T (2009) Perspectives of gene expression profiling for diagnosis and therapy in haematological malignancies. Brief Funct Genomic Proteomics 8: 184-193.

11 Nebbioso A, Carafa V, Benedetti R, Altucci L (2012) Trials with 'epigenetic' drugs: An update. Mol Oncol 6: 657-682.

12 Burke MJ, Bhatla T (2014) Epigenetic modifications in pediatric acute lymphoblastic leukemia. Front Pediatr 2: 42.

13 Gallipoli P, Giotopoulos G, Huntly BJ (2015) Epigenetic regulators as promising therapeutic targets in acute myeloid leukemia. Ther Adv Hematol 6: 103-119.

14 He S, Roberts A (2008) Targeted therapies in hematological malignancies. In: Targeted and individualized therapies. Edited by: Solomon B and Zalcberg J. Cancer Forum 32: 3.

15 Costello C (2017) An update on role of daratumumab in the treatment of multiple myeloma. Ther Adv Hematol 8: 28-37.

16 Taylor J, Xiao W, Abdel-Wahab O (2017) Diagnosis and classification of hematologic malignancies on the basis of genetics. Blood 130: 410-423.

17 Chen Z (2008) Molecular cytogenetic markers related to prognosis in hematological malignancies. World J Pediatr 2: 252-259.

18 Nybakken GE, Bagg A (2014) The genetic basis and expanding role of molecular analysis in the diagnosis, prognosis, and therapeutic design for myelodysplastic syndromes. J Mol Diagn 16: 145-158.

19 Foà R, Del Giudice I, Guarini A, Rossi D, Gaidano G (2013) Clinical implications of the molecular genetics of chronic lymphocytic leukemia. Haematologica 98: 675-685.

20 Harrison CJ (2009) Cytogenetics of paediatric and adolescent acute lymphoblastic leukaemia. Br J Haematol 144: 147-156.

21 Miles RR, Shah RK, Frazer JK (2016) Molecular genetics of childhood, adolescent and young adult non-Hodgkin lymphoma. Br J Haematol 173: 582-596.

22 Janz M, Mathas S (2008) The pathogenesis of classical Hodgkin's lymphoma: What can we learn from analyses of genomic alterations in Hodgkin and Reed-Sternberg cells? Haematologica. 93: 1292-1295.

23 Harada H, Harada Y (2015) Recent advances in myelodysplastic

syndromes: Molecular pathogenesis and its implications for targeted therapies. Cancer Sci 106: 329-336.

24 Lohr JG, Stojanov P, Carter SL, Cruz-Gordillo P; Multiple Myeloma Research Consortium, et al. (2014) Widespread genetic heterogeneity in multiple myeloma: Implications for targeted therapy. Cancer Cell 25: 91-101.

25 Küppers R (2012) New insights in the biology of Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program. 2012: 328-334.

26 Verma R, Kumar L (2015) Molecular biology of multiple myeloma. J Hematol Transfus 3: 1035.

27 Tiacci E, Penson A, Schiavoni G, Ladewig E, Fortini E, et al. (2016) New recurrently mutated genes in classical Hodgkin lymphoma revealed by whole-exome sequencing of microdissected tumor cells Blood 128: 1088.

28 Falini B, Martelli MP, Tiacci E (2016) BRAF V600E mutation in hairy cell leukemia: from bench to bedside. Blood 128: 1918-1927.

29 Raetz E (2017) Tectonic shifts in the 2016 treatment landscapes for acute lymphoblastic leukemia. Hematologist, American Society of Hematology, ASH News and Reports 14: 1.

30 Owen C, Assouline S, Kuruvilla J, Uchida C, Bellingham C, et al. (2015) Novel therapies for chronic lymphocytic leukemia: A Canadian perspective. Clin Lymphoma Myeloma Leuk 15: 627-634.e5.

31 Moss P (2017) BTK inhibition saunters to the front of the line in CLL. Hematologist, American Society of Hematology, ASH News and Reports. 14: 1.

32 LaCasce AS (2017) The evolution of immunotherapy in lymphoma. Hematologist, American Society of Hematology, ASH News and Reports. 14: 1.

33 Derenzini E, Younes A (2011) Predicting treatment outcome in classical Hodgkin lymphoma: Genomic advances. Genome Med 3: 26.

34 Kasamon YL, de Claro RA, Wang Y, Shen YL, Farrell AT, et al (2017) FDA approval summary: Nivolumab for the treatment of relapsed or progressive classical Hodgkin lymphoma. Oncologist 22: 585-591.

35 Sorge CE, McDaniel JK, Xavier AC (2016) Targeted therapies for the treatment of pediatric non-Hodgkin lymphomas: Present and future. Pharmaceuticals (Basel) 9. pii: E28.

36 Pettirossi V, Santi A, Imperi E, Russo G, Pucciarini A, et al (2015) BRAF inhibitors reverse the unique molecular signature and phenotype of hairy cell leukemia and exert potent antileukemic activity. Blood 125: 1207-1216.

37 George TI, Allen MB (2017) The year's best in myeloproliferative neoplasms. Hematologist, American Society of Hematology, ASH News and Reports 14: 1.

38 Driscoll JJ, Ludtka T (2015) The promise and challenges of personalized medicine in hematologic malignancies. J Hematol Thromb 1: 3.

39 Lai C, Karp JE, Hourigan CS (2016) Precision medicine for acute myeloid leukemia. Expert Rev Hematol 9: 1-3.

40 Talor J, Abdel-Wahab O (2017) Progress and promise: Precision medicine for patients with acute myeloid leukemia. Hematologist, American Society of Hematology, ASH News and Reports 14: 1.

41 Ebert BL (2017) Introduction to a review series on precision hematology. Blood 130: 408-409.