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Introductory Chapter: Advances in Hematologic Malignancies

Gamal Abdul Hamid and Fadhel Hariri

1. Introduction

Hematological malignancies contain an accumulation of heterogeneous conditions, by which is commonly affect old ages, as the median age for most of these diseases all originating from cells of the bone marrow and the lymphatic system. There are three noteworthy gatherings: lymphomas, leukemia and plasma cell neoplasms. European patients with hematological malignancies have improved over the previous decade, most likely as a result of new medications, for example, imatinib in chronic myeloid leukemia and rituximab in lymphomas [1].

In developed countries and developing countries hematological malignancies (HMs) are differs and account about 8–9% of all cancers, being the fourth common cancer in developed countries [2]. The leukemia incidence rates are 24.5 per 100,000 is 8.8% in the US, 6.3% in Jordan, 5.4% in Egypt [3] The lymphoma incidence rate have been reported to be high in Canada (27.7%), Australia (25%) and Western Europe (17.9%), moderate (10.2%) in Middle East and Africa and low (6.5%) in East Asia [3].

While the previous 20 years witnessed an explosion in the quantity approved treatments for lymphoid and myeloid malignancies and few medications were endorsed, especially for leukemia, lymphoma and myeloma. This was astounding in light of comparable, if not more prominent, propels in the comprehension of the genetic basis and pathophysiology of hematological malignancies, which account 8–24% of every single grown-up disease [1]. The test of making an interpretation of these logical revelations into powerful treatments for patients with hematological malignancies established as an urgent unmet medical need.

2. Molecular diagnosis in hematological malignancies

Hematological malignancies are heterogeneous in both clinical and biological aspects. The association of genomic profile changes associated with hematological malignancies is complex and variable including translocations, karyotypic improvements, transformations and adjustments of post-translational alteration and some genetic changes are needed, to induce the onset of disease. This proof in relationship with the development of molecular techniques has prompted an alteration of the current authoritative opinion concentrating on a solitary quality or single pathway analysis [4].

The advancement in molecular biology techniques has not just permitted the individualized molecular diagnosis of hematological malignancies but have also prompted the disclosure of genetic or targeted therapeutic schemes with cytotoxic, anti-metabolic or immunomodulatory properties [4].

Utilizing karyotype analysis and the new technique of polymerase chain reaction (PCR), chromosomal microarrays (CMA), fluorescence in situ hybridization (FISH)

and new generation sequencing technique (NGS), it is conceivable to configuration better hazard stratification classes and decide if there is complete remission or presence of minimal residual disease (MRD).

New molecular and cytogenetic methods have been connected to determination of diagnosis and treatment. As to, the reasonableness of those strategies expands the precision and the speed of results while screening can be even more successfully performed. In regard to treatments, immunomodulatory and target therapies assurance better outcomes with less hematological side effects.

The molecular basis of hematological malignancies has developed aberrant genes expression and/or pathological expression of natural genes [5]. Also other new somatic mutations detected by Next Generation Sequencing NGS have prompted the revelation of already unknown molecular and pathological genes as well as diagnostic and therapeutic value [6].

Genetic changes plays a vital role to diagnose and classify the stage of disease and determine the prognosis of diseases and choice of treatment in most hematological malignancies [7–9]. Molecular diagnostic technology in patients with HMs is useful for diagnosis and prognosis and selecting the proper treatment, and to monitor the degree of response to new therapies [5, 8].

The majority of leukemia, specifically predictable by gene expression profiles [9]. Vulnerability tests are being developed through the explicit treatment of targeted therapies such as imatinib in acute lymphoblastic leukemia BCR-ABL positive (ALL) and farnesyltransferase inhibitors in acute myeloblastic leukemia (AML) [10].

Myelodysplastic syndrome (MDS) and acute leukemia (AML and ALL) are intensely influenced by epigenetics [11]. Targeted epigenetic therapies may be particularly attractive as long-term treatment in post remission period, if they could target certain subclones once standard chemotherapy has produced targeted cytoreduction to induce remission of acute leukemia [12]. Personalized targeted therapy have just upset treatment results in some HMs, especially, chronic myeloid leukemia (CML), non-Hodgkin's lymphoma (NHL), multiple myeloma (MM) and acute promyelocytic leukemia (APL) [12, 13].

3. Detection of molecular markers in hematologic malignancies

The molecular markers and genetic studies in hematologic malignancies include: (1) **AML:** FLT3-ITD, CEBPA, RUNX1, NPM1, PML-RARA, ASXL1, IDH1, IDH2, DNMT3A, TET2 and BCR-ABL1; (2) **ALL:** IKZF1, CDKN2A/B, BCR-ABL1, BCR-ABL1-like, NOTCH1, ETV6, and RUNX1; (3) **chronic myeloproliferative (CMPNs):** CAL-R, MPL, JAK2, SRSF2, SETBP1, TP53, CSF3R and ASXL1; (4) **CML:** BCR-ABL1; (5) **MDS:** RUNX1, JAK2, EZH2, SF3B1, IDH1/2, N-RAS, TP53, TET2, KIT, SRSF2, and ASXL1; (6) **CLL:** ATM, TP53, BIRC3, del11q, SF3B1 and NOTCH1 mut; (7) **Hodgkin's lymphoma (HL):** BCL6, SOC1, JUNB, MAP3K14, STAT6, MDM2, JAK2, XPO1, NFKBIE, GNA13, MAFB, IKBA, TNFIP3, BCL3, NFKBIA, PD-L1, PD-L2, and REL6; (8) **B-cell lymphomas:** MYC/BCL2, MYC/BCL2/BCL6, SOX11, CCND1/2, CCND3 and TCF3; (9) **T-cell lymphomas:** TP63, IRF4, DUSP22 and ALK; (10) **Hairy cell leukemia (HCL):** BRAFV600E, IGHV4-34, MAP2K1; and (11) **MM:** KRAS, CCND1, CCND2, CCND3, TP53, DI53, NRAS, MAF, FAM46C and BRAF [5, 10, 14–17].

4. Personalized target therapy: Monoclonal antibodies

In the late 1970s, the technology development of monoclonal antibody (MoAb) was possible to produce antibodies targeting specific antigens to the surface of cancer cells. The antibodies target an antigen present at high concentrations on cancer cells

and missing or present at low fixations on typical cells. The MoAbs, is given as monotherapy or target therapy with chemotherapy, have excellent outcome in different types of neoplasm's with improve quality of life and survival rate and time. An assortment of components has been proposed that would allow monoclonal antibodies to kill cancer cells, including apoptosis, inhibition of cell growth, cellular cytotoxicity.

The development of molecular and genetic technology play important role in the modernization and modification of the (2016 WHO Edition) for classification of tumors of hematopoietic and lymphoid tissues, is being published by World Health Organization, the aims to provide these data with essential clinical characteristics, morphology and immunophenotyping relevant to targeted and novel therapies against incurable diseases [18].

The targeted and novel therapies currently used in the treatment of hematological malignancies are: (1) Acute myeloblastic leukemia subtypes: lintuzumab, midostaurin, gemtuzumab, ulocuplumab, sorafenib, navitoclax, panobinostat, vorinostat, Dr383-IL3 and lestaurtinib; (2) acute myeloblastic leukemia (promyelocytic type): all trans-retinoic acid gemtuzumab ozogamicin and arsenic trioxide; (3) acute lymphoblastic leukemia: tyrosine kinase inhibitors, rituximab, inotuzumab ozogamicin, nelarabine, blinatumomab, and CAR T-cells; (4) myelodysplastic syndrome: azacitidine, decitabine, and lenalidomide; (5) chronic myeloid leukemia: imatinib, nilotinib, dasatinib and ponatinib; (6) chronic myeloproliferative neoplasms: ruxolitinib; (7) chronic lymphatic leukemia (CLL): rituximab, idelalisib, ibrutinib, venetoclax obinutuzumab, and duvelisib; (8) HL: brentuximabvedotin, nivolumab, rituximab and everolimus; (9) B-cell lymphomas: tositumomab, rituximab, ibritumomab tiuxetan and CAR T-cells; (10) T-cell lymphomas: romidepsin, alemtuzumab, epratuzumab, denileukin and nelarabine; (11) hairy cell leukemia: vemurafenib; and (12) multiple myeloma: bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab milatuzumab, and ixazomib [17–26].

The targeted treatments are directed to the cancer cell and do not harm or affect the healthy cell, which is of course a breakthrough in the treatment of hematological malignancies, but is still in the process of research despite the success of the experiments, which have been conducted and targeted therapies exist for many types of cancers, including: Chronic leukemia and lymphoma is used in making there are opportunities for no need for bone marrow transplantation, and targeted therapies have proven to be a great success.

5. Examples of advance treatment in AML

5.1 Enasidenib for IDH-mutated AML

Mutations in isocitrate dehydrogenase (IDH) occur in 20% of AML cases and are also found in gliomas and cholangiocarcinomas. Enasidenib was approved in August 2017 by FDA for treatment acute myeloblastic leukemia patients (AML) refractory or relapsed to chemotherapy with presence of IDH2 mutation. IDH2 mutations are relatively common in hematological malignancies, which occur in ~12% of AML patients [27]. The follow up of patients for a period of 6.6 months, 23% of patients experienced a complete remission [28]. The dose of enasidenib is 100 mg once daily and continuously was chosen for the extension stage.

5.2 Gemtuzumab ozogamicin for CD33+ AML

Gemtuzumab ozogamicin (Mylotarg) is an antibody-drug conjugate to treat patients who are more than 60 years old in first relapse AML with CD33+ and not candidates for chemotherapy and also for pediatric patients, more than 2 years old

with relapsed or refractory CD33+ AML. Subsequent studies with positive findings resulted in the resurrection of gemtuzumab ozogamicin and its approval in 2017.

5.3 Midostaurin in *FLT3*-mutated AML

Midostaurin was approved on 28 April 2017 by FDA for patients with AML who had *FLT3* mutations. Midostaurin is an oral small molecule *FLT3* inhibitor that inhibits wild-type and mutant *FLT3* kinases as well as a number of other factors. The recommended dose of midostaurin is 50 mg capsules given twice daily on days 8–21, with cytarabine (200 mg/m²), continuously for 7 days (d1–7) and 60 mg/m² daunorubicin for 3 days on (d1–3) and also repeat same dose of midostaurin daily for 2 weeks (day 8–21) in each cycle of consolidation in combination with high dose of cytarabine [29].

6. Some target therapy experience in lymphoproliferative neoplasms

6.1 Rituximab in the treatment of non-Hodgkin's lymphoma

Rituximab (RTX), a chimeric mouse anti-human monoclonal antibodies (MoAbs) targets the CD20 antigen expressed on the neoplastic B cells of leukemia and lymphoma. Rituximab approved by FDA in 1997 for the treatment of B-cell CD20 positive relapsed and refractory of indolent follicular lymphoma, and the European Medicines Agency approved rituximab in June 1998 for chemoresistant or relapsed NHL and for therapy of patients with stage III/IV [7].

The expression of CD20 varies according to type of cancer (expression in follicular lymphoma is very high, while in chronic lymphocytic leukemia is low). The R-CHOP combination chemotherapy protocol (rituximab, cyclophosphamide, oncovin, adriamycin and prednisone) has shown better survival than CHOP alone for treatment of high grade diffuse large cell lymphoma (DLBCL).

6.2 Alemtuzumab for *patients* chronic lymphocytic leukemia

Alemtuzumab is a recombinant humanized immunoglobulin MoAb that targets the cell-surface CD52 antigen, has indicated promising outcomes. CD52 is expressed at high levels on normal healthy cells and on CLL cells. Alemtuzumab initially received FDA-approval in September 2007 for treatment of B-CLL patients who are refractory to chemotherapy (fludarabine-*refractory* CLL) [30].

6.3 Milatuzumab in the treatment of multiple myeloma

Milatuzumab is an anti-CD74 monoclonal antibody that expresses the CD47 antigen.

Anti-CD47 antibodies have emerged in recent years as a new class of checkpoint inhibitors that may be useful target therapy of hematological malignancies and more effective in treatment of MM, CLL and NHL [31]. Milatuzumab in single monotherapy or in combination with bortezomib is very effective in multiple myeloma.

6.4 Epratuzumab

Epratuzumab targets the CD22 antigen on B lymphocytes and has additionally been utilized against refractory or relapsed DLBCL patients to rituximab and can be given as monotherapy or in combination with rituximab or standard chemotherapy achieved complete remission in 60% of patients [32].

6.5 Inotuzumab ozogamicin for Philadelphia+ ALL

Like gemtuzumab ozogamicin, inotuzumab ozogamicin (Besponsa), an antibody/chemotherapy conjugate that internalizes into the tumor cells upon binding to CD22 on the cell surface. “It’s carrying a CD22 Trojan horse to the cell, discharging the payload there (the microtubule-targeting agent calicheamicin) is a highly potent chemotherapeutic drug belonging to the enediyne class of DNA-damaging cytotoxic agents derived from the soil bacterium *Micromonospora echinospora* ssp. *calichensis*.” Inotuzumab looks encouraging in a number of lymphomas, yet it came to advertise first for relapsed or refractory B-ALL patients. The pivotal multicenter stage III preliminary selected 326 patients with refractory or relapsed ALL CD22+, randomizing them to a standard treatment or inotuzumab ozogamicin [33]. Its recent approval has greatly increased the ability to attain remission long period and represents a significant advance in therapeutic options for treatment of relapsed ALL.

6.6 Copanlisib for follicular lymphoma

In September, 2017, Copanlisib was approved by the FDA used to treat of adult patients with recurrent low grade follicular lymphoma who have received at least two previous chemotherapies. Copanlisib is a class I phosphatidylinositol 3-kinase (PI3K) inhibitor with a predominance of PI3K- α and PI3K- δ activity present in cancerous B cells [34].

6.7 Ibrutinib in chronic graft-vs.-host disease (GVHD)

In 2017, ibrutinib (Imbruvica) was approved as the first drug for GVHD after corticosteroid therapies response failure. Ibrutinib is a small-molecule of the B-cell antigen receptor inhibits cell proliferation, and promotes apoptosis of cancer cells through inhibition of Bruton’s tyrosine kinase. The daily oral dose of 420 mg with median time response of 12 weeks and overall response rate about 67% [35].

7. CAR T-cell therapy

In fact, the new therapeutic progress of chimeric antigen receptor T cell is simultaneously a genetically, mechanically, and cellular therapy. This technique changed the leukocytes of the patient in such a way that they could identify and destroy the cancer cells. Despite a number of side effects, CAR T-Cell therapy will be effective for most patients who do not accept any other treatment or in relapses.

The purpose of CAR creation is to attack specific target molecules on the surface of cancer cells. They are usually antigens CD19 and CD22, which are designated for malignant cells in leukemia and lymphoma. It is very important that there are no similar molecules on the surface of healthy cells. The patient’s own T cells are designed to show antigen receptors as “warheads” to focus on and assault tumor cells tumor cells when infused back into the patient. At the point when T cells perceive their target, they are activated, prompting the release of natural killer cells, cytokines, cytotoxic T lymphocytes, and other effector components.

The test of these engineered cells is to avoid inhibitor and suppressive signals from regulatory immune cells, the target cells, and the tumor microenvironment. It is beneficial to make reference to that CAR-T cell can recognize potential antigens in almost all structures including lipid, carbohydrate and protein antigens, which can be joined explicitly by antibodies [36, 37].

To make a situation where the CAR T cells will be respected, the patient experiences lymphodepleting treatment with fludarabine and cyclophosphamide. A couple of days after the fact, the T-cell item is transfused into the patient, where CD8+ and CD4+ cells will extend and endure until the tumor is dispensed with. Whenever effective, this procedure prompts long-term remission [38, 39].

In August 2017, a number of large clinical trials of the new cancer treatment technique, CAR T-cell, were completed. According to their findings, two drugs were approved by FDA: tisagenlecleucel (Kymriah) and as the first synthetic therapy for relapsed or refractory B- ALL and the second product of CAR T-cell therapy is axi-cabtagene ciloleucel (Yescarta), as immunotherapy for adults patients whose large cell lymphoma in refractory or relapsed on other therapies, including high-grade large cell lymphoma (mediastinal or transformed from follicular lymphoma) [38].

The improvement method of treatment with of CAR T cell therapy requires experience in many areas, including biology, molecular biology, antibody technology, regulatory requirements, and more. Increasing collaboration among key specialists from universities, research centers, and stakeholders will enhance the success of these drugs [39].

8. Bone marrow transplantation

Bone marrow transplantation is an important branch and important indicator of the treatment model of hematologic malignancies. Hematopoietic stem cell transplantation (HSCT) has been included in therapeutic guidelines for most malignant tumors [40]. For those diseases that can be treated by a conventional therapy, how many of the acute leukemia and aggressive lymphomas and allogeneic BMT they are often the preferred treatment, if the initial relapse. For hematologic malignancies curable with a conventional therapy, such as multiple myeloma, myelodysplastic syndromes and low-grade lymphoma and acute leukemia poor risk, usually the treatment will be allogeneic BMT treatment at the time survival duration is felt to be relatively short.

Author details

Gamal Abdul Hamid^{1*} and Fadhel Hariri²

1 Faculty of Medicine, Aden University, Aden, Yemen

2 Ministry of Public Health, Aden, Yemen

*Address all correspondence to: drgamal2000@yahoo.com

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