Recent Advances in Haematology

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ABSTRACT

The advent of different techniques as well as different randomized clinical trial has led to many advances in the discipline of haematology. Recently in the year of 2019 and 2020, new advances have been observed both in the diagnosis and management of haematological disorders.

Key words: Recent advances, Haematology

Introduction

Haematological disease, whether it is fierce or slothful, affects patients of all ages irrespective of sex, race, ethnicity and religion with varied and numerous clinical presentations. Diverse biological and clinical behaviours characterise both benign and malignant haematological disorders. These haematological disorders are associated with variable and complex molecular alterations at the genomic level. The various genomic and molecular alterations include mutations, translocations, karyotype abnormalities and rearrangement as well as many post-translational modifications which in most cases are required to initiate the disease onset.¹ Such genomic alterations are now possible to detect by using Polymerase Chain Reaction (PCR), karyotype analysis, fluorescence in situ hybridization (FISH) and next generation sequencing (NGS). Now it is possible to contemplate risk stratification and determine minimal residual disease (MRD) by adopting these techniques. Immune checkpoint inhibitors, antibodies and chimeric antigen receptor (CAR)-T cells can guide most efficient therapeutic strategies. The aim of this review is to evaluate and analyse the recent development in haematology,

their molecular basis and recent additions in the last six months.

ACUTE LEUKAEMIA AND MYELODYSPLASTIC SYNDROME

Ivosidenib for treatment of older adults with IDH1-mutant AML

Conventional intensive induction therapy is challenging for older adults with acute myeloid leukaemia (AML) but the presence of serviceable mutations in genes such as isocitrate dehydrogenase-1 may offer an opportunity for less toxic treatment. Single agent, oral ivosidenib achieved complete remission in nearly one-third, with

median survival more than one year was found in a study which included 34 older adult patients with IDH1-mutant AML who were ineligible for intensive induction therapy. With this single agent treatment, nearly half of affected patients did not require blood transfusion. However, less than ten percent patients developed differentiation syndrome (DS) but did not require treatment; therapy was otherwise well tolerated. USA FDA approved this single agent oral ivosidenib for patients' ≥ 75 years with IDH1-mutant AML. The side effects of using this drug are the development of DS, prolongation of QT interval and rare cases of Guillain-Barre syndrome. Comparing the risk-benefit

oral ivosidenib may be an acceptable treatment for older adults with IDH1-mutant AML.²

Luspatercept for MDS with ring sideroblasts

Well defined treatment for myelodysplastic syndrome with ring sideroblasts (MDS-RS) does not have a reasonable guideline but this disease has favourable prognosis. Luspatercept is a novel erythroid maturation agent that can improve anaemia by binding transforming growth factor (TGF) beta ligands. In a phase 3 trial in patients with MDS-RS who were unlikely to respond to erythropoiesis stimulating agents (ESA), luspatercept was well tolerated and was superior to placebo for achieving transfusion-independence. Luspatercept is approved by the US Food and Drug Administration for anaemia associated with MDS-RS.³

Measurable residual disease in AML

To predict future relapse after completion of treatment of acute myeloid leukaemia, it is important to identify measurable residual disease (MRD) by sensitive molecular or immunologic techniques which are emerging as a powerful means of identifying persisting acute myeloid leukaemia (AML) after treatment. In a multicentre study that included more than 150 patients who were treated for RUNX1-RUNX1T1-rearranged AML, detection of MRD, using quantitative polymerase chain reaction (Q-PCR) for RUNX1-RUNX1T1 transcript levels in blood or bone marrow, was predictive of overall survival and relapse. The importance of MRD detection is obvious with this and previous studies and this method confirms for assessing prognosis in AML. However, MRD assays must be standardized and validated prior to their routine clinical use in treatment decisions for AML.⁴

ANAEMIA AND OTHER RED CELL DISORDERS

Luspatercept for beta thalassemia

Thalassaemia is a chronic haemolytic anaemia and regularly requires transfusion especially in beta thalassaemia major or double heterozygous haemoglobin defects. Such chronic transfusion in these patients lead to various complications such as iron overload, bronze diabetes mellitus and the requirement for routine intravenous access. Luspatercept is one of the agents that are important for red cell maturation though the mechanism is not completely understood. In a randomized control trial in 336 adults suffering from transfusion dependent beta thalassaemia, luspatercept reduced transfusion need significantly compared with placebo. Luspatercept is indicated for adults with transfusion-dependent beta thalassaemia, splenectomised individuals treated with luspatercept should also receive thromboembolism prophylaxis.⁵

New ASH guideline for transfusion in sickle cell disease

Sickle cell disease is a type of haemoglobinopathies and it has various clinical presentation and complication as well as requires regular blood transfusion. The American Society of Hematology (ASH) has issued a new guideline on transfusion in sickle cell disease. The new guideline includes the use of extended antigen matching blood for transfusion to minimize alloantibodies, use of automated exchange transfusions rather than simple or manual exchange transfusions in chronically transfused patients to reduce iron overload and use of exchange transfusion rather than simple transfusion in acute chest syndrome to rapidly lower the haemoglobin S percentage.⁶

CHRONIC LEUKAEMIA AND THE MYELOPROLIFERATIVE NEOPLASMS

CAR-T therapy in relapsed chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is a monoclonal disorder characterized by a progressive accumulation of functionally incompetent lymphocytes. CLL is the most common form of leukaemia found in adults in western countries.⁷ Patients with CLL who have relapsed after conventional therapy may be a potential candidate for an investigational treatment by CD19-directed chimeric antigen receptor (CAR) -T cell therapy. In a study which included 32 patients with relapsed or refractory CLL, 28% achieved a complete response. CAR therapy was not influenced by the patient age, prior therapies or tumour genetics. Though few serious complications were reported but there was no evidence of CAR therapy related death.⁸

Next-generation sequencing for BCR-ABL1 mutation detection in CML

Chronic myelogenous leukaemia (CML), also known as chronic myeloid leukaemia, is a myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate. Recently patients with chronic myeloid leukaemia (CML) are experiencing a suboptimal response to a tyrosine kinase inhibitor (TKI), detection of a mutation in the BCR-ABL1 kinase domain (KD) may prompt a change in therapy. However, conventional Sanger sequencing (SS) detects a KD mutation in only a minority of such patients. A prospective study of more than 200 consecutive patients with a suboptimal response to TKI therapy directly compared SS with next-generation sequencing (NGS) for mutation detection. KD mutations were detected in one-quarter of patients by SS, but in nearly half by NGS; moreover, NGS detected

low-level mutations known to cause TKI resistance in one-fifth of those who were negative for mutations by SS. While NGS is not widely applied for KD mutation detection at present and the clinical importance of low-level mutations is uncertain, NGS may offer more sensitive and earlier detection of actionable BCR-ABL1KD mutations.⁹

Asciminib for multiply relapsed chronic phase CML

Patients with chronic phase chronic myeloid leukaemia (CP-CML) who is refractory to, relapses after or is not tolerated of ≥ 2 prior tyrosine kinase inhibitor (TKI), their next appropriate treatment is not still well defined. Asciminib is an allosteric inhibitor of BCR-ABL1 that binds to the myristoyl site, in contrast with other TKIs that bind the ATP binding site. In a study of 141 patients whose CP-CML was not controlled after ≥ 2 prior ATP-competitive TKIs, in such cases asciminib was active and well-tolerated. More than 90 percent patients showed haematologic response to asciminib and among half of them had a complete cytogenetic response. However, still therapy with asciminib was not approved by the regulatory body for routine clinical use in multiply relapsed CP-CML.¹⁰

HAEMOSTASIS AND THROMBOSIS

Oral anticoagulants and fracture risk

Oral anticoagulant warfarin is associated with increased risk of fracture, especially vertebrae and ribs among older women chronically taking this drug.¹¹ When compared with apixaban (direct oral anticoagulant) [DOAC] and warfarin, it was found in two large retrospective studies that individuals with atrial fibrillation taking DOAC had lowered risk of fracture and the reason of such difference is not clear.¹²⁻¹³

Time of day for taking warfarin

Clinicians usually advise patients to take warfarin in the evening but the appropriate timing of warfarin administration is unknown. In a study including 200 people who were taking warfarin for at least three months and were randomly assigned to continue with evening or switch to morning dosing, there was no difference in the time in the therapeutic range (TTR), a widely used measure that correlates with clinical outcomes. This trial provides reassurance that warfarin can be taken at any time of day once a stable dose has been established.¹⁴

Emicizumab in children with haemophilia A

Emicizumab, a monoclonal antibody that substitutes for the function of factor VIII, was shown to provide effective

prophylaxis in adolescents and adults with haemophilia. The drug was also found safe and effective in children. Emicizumab is administered subcutaneously one or more weeks interval, allowing many of the children in the trial to have their central venous access catheters removed.¹⁵

Investigational anticoagulant targeting factor XIa

An investigational monoclonal antibody directed against factor XIa is Osocimab. It was observed in a randomized clinical trial in over 800 individuals undergoing elective knee arthroplasty where osocimab was compared with enoxaparin or apixaban showed that osocimab 1.8 mg/kg preoperatively had similar rates of preoperatively venous thromboembolism (VTE) and bleeding as apixaban but lower rates of VTE and bleeding than enoxaparin. The half-life of osocimab is 30 to 44 days, allowing single-dose administration for surgical prophylaxis.¹⁶

Gene therapy for haemophilia

Gene therapy is an experimental technique that uses genes to treat or prevent disease.¹⁷ Such therapy for haemophilia with adeno-associated virus (AAV) vectors is promising. In a study involving 15 men with severe haemophilia A was treated with an AAV5-based factor VIII construct showed reduced bleeding with increased factor VIII activity (mean activity 20 percent) at three years.¹⁸ Another study which includes three men with severe haemophilia B treated with AAV5-based factor IX construct demonstrated no bleeds and a mean factor IX activity of 47 percent at 26 weeks.¹⁹

Adjusted D-dimer for patients at low risk for pulmonary embolism

More than 1300 patients with suspected pulmonary embolus were evaluated in a prospective study. It was found that none had developed symptomatic venous thromboembolism when a protocol was used that included D-dimer adjusted for clinical probability by Wells score (D-dimer $<1000\text{ng/mL}$ for low probability and <500 for moderate probability). By using Wells score, computed tomographic pulmonary angiographic imaging was reduced by an about 17%.²⁰

LYMPHOMAS: HODGKIN AND NON-HODGKIN

Narrowed indications for bone marrow biopsy in staging follicular lymphoma

Follicular lymphoma (FL) is typically a slow-growing or indolent form of non-Hodgkin lymphoma (NHL) that arises from B-lymphocytes, making it a B-cell lymphoma. This lymphoma subtype accounts for 20 to 30% of all NHL cases. Follicular lymphoma is usually not considered to be curable, but more of a chronic disease. Patients can

live for many years with this form of lymphoma.²¹ FL stage I are the most suitable candidate for radiation (RT) therapy which is curative in a small percentage of patients. Bone marrow biopsy is one of the methods used for staging lymphoma. Patients suspected of harbouring stage I FL, unilateral bone marrow biopsy is performed to rule out bone marrow involvement, a finding that would make them incurable with RT. In contrast, several recent studies have shown that bone marrow biopsy, at baseline and after treatment, very rarely impact the staging and response assessment of patients with advanced stage disease on imaging. Based on these findings, bone marrow biopsy is no longer routinely performed in patients with advanced stage disease on imaging.²²

Maintenance therapy for advanced stage follicular lymphoma

Some experts offer two years of maintenance with an anti-CD20 monoclonal antibody for patients with previously untreated advanced stage follicular lymphoma receiving chemo immunotherapy. In a largest randomized trial to address maintenance in this population (PRIMA), initial results demonstrated an improvement in progression-free survival (PFS) relative to observation but higher rates of adverse events. A final analysis with nine years of follow-up confirmed a PFS benefit (median 10.5 versus 4 years) and reported similar overall survival (80 percent at 10 years) and quality of life ratings in the two arms.²³

CAR-T cell therapy for relapsed or refractory mantle cell lymphoma

Survival after salvage chemotherapy for relapsed or refractory (r/r) mantle cell lymphoma (MCL) is not well defined. Optimal treatment for such patients is also not well established. In a multicentre study with 60 patients, a single treatment with anti-CD19 chimeric antigen receptor (CAR)-T cells achieved a complete response in two-thirds and median survival was more than one year. Grade ≥ 3 cytokine release syndrome and neurologic events occurred in 15 and 31 percent of patients, respectively but none of these episodes was fatal; grade ≥ 3 cytopenia and infections were common, including two fatal infections.²⁴

Less chemo immunotherapy for limited stage diffuse large B cell non-Hodgkin lymphoma (DLBCL) with no adverse features

Patients with stage I or stage II diffuse large B cell non-Hodgkin lymphoma (DLBCL) without B symptoms has an excellent prognosis when treated with the current standard approaches of either six cycles of R-CHOP

(rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) or three cycles of R-CHOP followed by radiation therapy (RT). A randomized clinical trial was performed on 600 patients ≤ 60 years with stage I or stage II DLBCL without B symptoms by four versus six cycles of R-CHOP to determine whether less chemo immunotherapy could lead comparable outcomes with less toxicity. In this study it was observed that there was less haematologic and non-haematologic toxicity with four cycles of R-CHOP, while three-year progression survival (PFS) and estimated five-year PFS and overall survival were similar compared with six cycles.²⁵

MULTIPLE MYELOMA AND OTHER PLASMA CELL DISORDERS

Subcutaneous formulation of daratumumab for multiple myeloma (May 2020)

In multiple myeloma, most trials have approved daratumumab as intravenous formulation with weight-based dosing. But recently US FDA has approved a fixed-dose subcutaneously administered formulation of daratumumab in combination with hyaluronidase. In one randomized clinical trial comparing these two formulations as monotherapy, daratumumab-hyaluronidase resulted in a similar overall response rate, progression-free survival with fewer infusion-related reactions. From this clinical and analysing the results and lower total administration burden, it is recommended the use of daratumumab-hyaluronidase rather than intravenous daratumumab.²⁶

Isatuximab in relapsed multiple myeloma

Monoclonal antibodies against CD38 (daratumumab) and SLAMF7 (elotuzumab) amplifies responses and improve progression-free survival (PFS) in relapsed multiple myeloma and represent a major advance. In a randomized trial that included patients with multiply relapsed MM, the addition of anti-CD38 monoclonal antibody isatuximab to pomalidomide plus dexamethasone was well tolerated and improved median PFS by approximately five months. Based on these and other data, US FDA approved this combination for patients who have received at least two prior therapies including linalidomide and a proteasome inhibitor.²⁷

Antibacterial prophylaxis for patients with multiple myeloma

Profound immunodeficiency is observed among patients with multiple myeloma and recurrent severe infections, especially during the first three months following diagnosis. In a multicentre randomized trial involving more than 950 adults with newly diagnosed MM, rates of febrile episodes (18 versus 23 percent) and mortality (0.8

versus 3 percent) were decreased with levofloxacin prophylaxis given for 12 weeks at the start of therapy compared with placebo.²⁸

Lenalidomide for high-risk smouldering multiple myeloma

Patients with smouldering multiple myeloma (SMM) have not given systemic treatment until recently and treatment deferred until progression to symptomatic disease. In a multicentre trial of 182 patients with SMM, single-agent lenalidomide improved progression-free survival and reduced end-organ damage (e.g., renal failure, bone lesions) when compared with observation. Serious (grade 3/4) adverse reactions occurred in 41% of patients in the treatment arm; there was one treatment-related death in the phase II run-in and none in the randomized phase. The PFS benefit was definitive in those with high-risk SMM but less clear in those with intermediate-risk disease. For patients with high-risk SMM, treatment with single-agent lenalidomide or Rd is recommended.²⁹

Conclusion

Medical science is a challenging subject and always superseded the previous study during the course of time or ideas in the management of patients which was clearly observed in this review article; although many recommendations still not approved by the competent authority but in the incoming days these new mode of management or therapies will possibly added in the treatment protocol of haematological diseases.

Conflict of interest: None.

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