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Haematology symposium report: an update for the general physician and the specialist

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ABSTRACT This symposium covered a wide range of topics of interest to both general physicians and specialists in haematology. Problems commonly encountered by acute physicians were explored, including the management of over-anticoagulation, thrombocytopenia associated with thrombosis and dealing with current and emerging risks of blood transfusion. Updates on the management of chronic lymphocytic leukaemia, multiple myeloma and Hodgkin's lymphoma were presented. The discovery of the JAK2V617F mutation and the use of tyrosine kinase inhibitors in chronic myeloid leukaemia have changed the way we diagnose and treat myeloproliferative disorders. New approaches to monitoring and treating transfusional iron overload were discussed. In the field of stem cell transplantation, the vogue for reduced intensity allogeneic transplants has allowed older patients to benefit from this treatment approach.

KEYWORDS Bisphosphonates, blood transfusion and risk, chronic lymphocytic leukaemia, deferasirox, heparin-induced thrombocytopenia, Hodgkin's lymphoma, imatinib, iron chelation, JAK2V617F mutation, osteonecrosis of the jaw, polycythaemia vera

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EDUCATION

SESSION 1 HAEMATO-ONCOLOGY UPDATE

Dr P Hillmen, Leeds Teaching Hospitals NHS Trust
Dr G Jackson, Royal Victoria Infirmary, Newcastle
Dr D Culligan, Aberdeen Royal Infirmary

Chronic lymphocytic leukaemia

Increased understanding of the molecular biology of chronic lymphocytic leukaemia (CLL) has led to the development of biological prognostic markers.

In the germinal centre, B cells undergo somatic mutation of the immunoglobulin heavy-chain variable-region genes. Survival of patients whose leukaemic cells have no somatic mutations is poor compared with those with mutations.[1,2]

Cytogenetic abnormalities also affect survival.[3] The 17p deletion (p53 mutation) confers resistance to conventional treatments such as alkylating agents and purine analogues, which use p53-dependent pathways to kill cells. Patients with mutated p53 respond better to high dose steroids and alemtuzumab.[4]

Fludarabine cyclophosphamide (FC) is the gold standard for treatment as it produces better complete remission rates than chlorambucil alone, although there is no difference in overall survival.[5] Conventional treatment can allow growth of p53 subclones, resulting in resistant disease at relapse. Patients who have detectable minimal residual disease following initial treatment may benefit from p53-directed therapy.[6]

Multiple myeloma and bisphosphonates

Bisphosphonates are recommended for all patients with symptomatic myeloma to prevent the progression of bone disease.[7] However, in recent years, osteonecrosis of the jaw has emerged as a complication of therapy.

Osteonecrosis of the jaw affects the mandible and/or maxilla.[8] It can present with localised pain (although a third of cases are painless[9]), altered sensation, loosening of teeth, infection of soft tissue or bone and pathological fracture. Risk factors include older age,[10] recent dental extraction or dental surgery,[8,11–13] poor oral hygiene and ill-fitting dentures. Osteonecrosis of the jaw is associated with the long-term use of bisphosphonates (>3 years)[11,13] and intravenous (iv) preparations, and is more common with zometa than pamidronate.[11,13,14]

Classical Hodgkin's lymphoma

Early-stage classical Hodgkin's lymphoma (CHL) (favourable and unfavourable disease) treated with two to four cycles of combination chemotherapy – usually doxorubicin bleomycin vinblastine dacarbazine (ABVD) – followed by involved field radiotherapy has an excellent outcome (progression-free survival [PFS]: 88% at seven years).[15] However, radiation increases the risk of secondary malignancies and cardiac and pulmonary toxicity. A negative positron emission tomography-computed tomography (PET-CT) following two cycles of ABVD may identify those patients who can be cured with chemotherapy alone.[16]

Advanced CHL is treated with six to eight cycles of ABVD. More intensive regimes improve PFS but have increased long-term toxicity.[17] PET-CT following two cycles of ABVD may be able to identify those patients who can be cured with ABVD and those who require more intensive primary treatment.

SESSION 2 EVOLVING CONCEPTS IN MYELOPROLIFERATIVE DISORDERS

Professor J Apperley, Hammersmith Hospital, London
Professor MF McMullin, Queen's University, Belfast

Chronic myeloid leukaemia and tyrosine kinase inhibitors

Six-year follow-up data from the International Randomized Study of Interferon and STI571 (IRIS)[18] shows that 400 mg of imatinib in chronic phase chronic myeloid leukaemia has a PFS of 93%, making imatinib the treatment of choice at diagnosis. However, about a third of patients fail on imatinib and require alternative treatment strategies.

Mutation analysis should be performed in patients who fail to achieve a complete haematological response at three months, those who fail to achieve a complete cytogenetic response at 18 months (with no decline in Philadelphia chromosome positivity) and those who lose their response to imatinib.[19]

Detection of mutations conferring resistance to imatinib requires a switch to a second-generation tyrosine kinase inhibitor. The T315I mutation, however, confers resistance to all tyrosine kinase inhibitors and therefore allografting should be considered in these patients.

Polycythaemia vera and the JAK2V617F mutation

In 2005 it was discovered that the majority of patients with polycythaemia vera (PV) have an acquired mutation affecting exon 14 of the Janus Kinase 2 gene (the JAK2V617F mutation). JAK2 is a tyrosine kinase that transduces signals from erythropoietin. Mutated JAK2 is constitutively active, leading to increased downstream signalling and dysregulation of haematopoiesis. Exon 12 mutations have been found in some patients with JAK2V617F-negative PV. The discovery of JAK2 mutations has simplified the diagnostic criteria for PV.[20]

SESSION 3 TO CLOT OR NOT TO CLOT: YOU DECIDE

Dr H Watson, Aberdeen Royal Infirmary
Dr RC Tait, Royal Infirmary, Glasgow

Anticoagulants

Up to 1.5% of the UK population are anticoagulated. The risk of bleeding on warfarin is associated with factors such as age, previous gastrointestinal bleed or stroke, recent myocardial infarction, renal impairment and anaemia.[21] The risk of major bleeding[22] increases significantly when the international normalised ratio (INR) rises above five.

For INRs >8 with no bleeding, warfarin should be withheld and vitamin K given. Oral vitamin K will bring the INR into the therapeutic range within 24 hours; iv vitamin K works within six hours. In life- or limb-threatening bleeding, a prothrombin complex concentrate will reverse anticoagulation immediately and iv vitamin K should also be given.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is characterised by a fall in the platelet count of 50% or more, 5–10 days after exposure to heparin. More than half of patients develop arterial or venous thrombosis. Heparin-induced thrombocytopenia is due to the development of IgG antibodies against an antigen on the platelet factor 4-heparin complex. The condition is more common in surgical patients and following use of unfractionated rather than low-molecular-weight heparin.

If HIT is suspected, its probability can be assessed using a scoring system.[23] If a high score is obtained, heparin should be stopped, an alternative anticoagulant commenced and a HIT antibody screen performed.

SESSION 4 UPDATES IN TRANSFUSION AND TRANSPLANTATION

Professor J Porter, University College London
Dr B McClelland, Strategy Director, Scottish National Blood Transfusion Service
Dr P Johnson, Western General Hospital, Edinburgh

Transfusional iron overload

Iron overload is an inevitable consequence of repeated blood transfusion. Cardiac iron deposition is the major cause of mortality in unchelated patients. Cardiac function can be assessed by echocardiogram, multiple gated acquisition scan or cardiac magnetic resonance imaging (MRI). A fall in ejection fraction >10% correlates with a high risk of developing left ventricular failure within 3.5 years.[24] This can be prevented by intensifying chelation. Cardiac iron can be measured using T2* MRI. T2* <20 milliseconds is associated with the development of left ventricular failure.[25]

Deferasirox is an oral iron chelator. Side effects include gastrointestinal disturbance and a non-progressive rise in serum creatinine on initiation of therapy. Unlike deferiprone, it does not cause cytopenias or arthralgia.

Blood transfusion and risk of pathogen transmission

Red cell transfusion carries a risk to the recipient. However, there is an expectation that transfusion should carry zero risk. This has led to the introduction of costly measures with only small safety gains, as seen with the

introduction of nucleic acid testing for hepatitis C. The emergence of new pathogens will require the introduction of further measures (donor screening tests for abnormal prion protein, prion filters) to reduce the risk of pathogen transmission.

Haematopoietic stem cell transplantation

Reduced intensity conditioning stem cell transplants involve the use of immunosuppressive rather than myeloablative conditioning, and their success depends on optimising the graft-versus-leukaemia effect. These 'mini-allografts' have a lower transplant-related mortality and can therefore be used in older patients.

Stem cells normally reside within the bone marrow attached to stromal cells. For use in transplantation, they are mobilised from the bone marrow using granulocyte-colony stimulating factor (G-CSF) and harvested from peripheral blood. AMD3100 (plerixafor) is a novel drug that interferes with the binding of stem cells to stromal cells, resulting in the release of stem cells into the peripheral blood. Plerixafor has been used successfully in patients who have failed G-CSF stem cell mobilisation.[26] It has also been used with G-CSF to significantly improve stem cell mobilisation.[27]

SUMMARY

The symposium was attended by both generalists and specialists, and the inclusion of interactive case-based presentations was well received.

EDUCATION

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