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DIAGNOSIS AND MANAGEMENT OF POLYCYTHAEMIA IN THE JAK2V617F ERA

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Background An erythrocytosis is defined by an increase in haemoglobin/haematocrit and an increased red cell mass. An absolute erythrocytosis can be classified on the basis of its aetiology into a primary process, where the bone marrow is the source of production of the excess red cell production, principally polycythaemia vera, or secondary, where red cell production is driven by some other process, and finally idiopathic, where the aetiology is unknown.

Methods or theme Mutations in the *JAK2* gene have now been demonstrated in the vast majority of patients who fulfil the diagnostic criteria for polycythaemia vera. The majority of mutations are in exon 14, but small numbers of different mutations have been found in some cases in exon 12. These findings have allowed the simplification of the diagnostic criteria.

Management has been directed at controlling cell counts and attempting to prevent complications, but new therapies targeted at the mutated gene may become available soon.

Causes of secondary erythrocytosis due to mutations in the genes in the oxygen-sensing pathway have been found in some rare familial cases, and provide insights into the control of erythropoietin production and the resulting erythrocytosis.

Conclusions Mutations of *JAK2* are present in most patients with polycythaemia vera, and their detection has simplified the diagnostic process. Management involves control of the myeloproliferation by venesection and cytoreduction, but new opportunities to inhibit *JAK2* will soon be available.

Further reading

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Keywords Idiopathic erythrocytosis, *JAK2* inhibitors, *JAK2* mutations, polycythaemia vera, secondary erythrocytosis
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MANAGEMENT OF CLASSICAL HODGKIN'S LYMPHOMA: UTILITY OF PET SCANNING

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Background The prognosis for most patients diagnosed at all stages with Hodgkin's Lymphoma (HL) is very good. In early stage patients, a limited course (2–4 cycles) of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) or 'ABVD-like' chemotherapy combined with involved field radiotherapy is superior to nodal radiotherapy alone. Using this approach German^{1,2} and French³ HL study groups have produced five-year progression-free survival and overall survival rates of >85% and >90% respectively. However, long-term toxicity includes second solid tumours and heart disease occurring within the radiation field. The big question in early stage HL, therefore, is whether the same cure rates can be maintained with chemotherapy alone.

In advanced stage HL the 'gold standard' therapy is 6–8 cycles of ABVD producing progression-free survival rates of 63–87%.⁴ The German HD9 study showed superior five-year progression-free survival rates of 82–92% with more intensive escalated BEACOPP chemotherapy, though with considerable acute and chronic toxicity.⁵ The big question in advanced stage HL, therefore, is whether patients can be stratified into those likely to be cured by ABVD and those who need intensification of therapy.

Methods and results Positron emission tomography (PET) scanning relies on malignant tissue taking up radio-labelled glucose more avidly than surrounding tissues. In HL, PET scanning improves the accuracy of staging and can distinguish metabolically active residual tumour from 'empty shell' residual tissue. End-of-treatment PET is predictive of relapse risk with a negative predictive value averaging 85%, possibly allowing omission of involved field radiotherapy in early stage patients who are PET-negative following ABVD.⁶ This is being tested in a current National Cancer Research Institute trial. Recent data from a combined Italian and Danish study has demonstrated that in advanced patients an early interim PET (post two cycles of ABVD) is a powerful predictor of outcome, and may

allow early stratification of advanced patients into good and bad responders to ABVD.⁷

References

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Keywords Bleomycin, dacarbazine, doxorubicin, Hodgkin's lymphoma, positron emission tomography, vinblastine
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Declaration of interests None declared.

BLOOD TRANSFUSION: MAKING IT SAFE AND EFFECTIVE

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Background In the last 25 years, blood transfusion has acquired a high public profile, largely related to viral (and more recently transmissible spongiform encephalopathy) infection, the publicity and legal claims often concentrating on allegations of failure to recognise and respond in a timely way to new or emerging threats.

Over the same period, there have been spectacular achievements in identifying the agents that cause transfusion-related infections, developing sensitive methods to detect them in the blood of asymptomatic donors and, perhaps most impressively, achieving very rapid and widespread implementation of these screening procedures. The result has been a dramatic reduction in the risks of infection with HIV, HTLV and hepatitis B and C due to transfusion.

Blood donation is widely seen and promoted as a humanitarian act, with publicity to encourage donation

bearing the general theme that blood is the 'gift of life'. However, the belief in the therapeutic properties of transfusion may be based in large measure on observations from an earlier era of medical technology. In recent years, and notably with the publication in 1999 of the first large clinical trial of red cell transfusions, investigators have begun to question the effectiveness of blood component transfusion in many clinical situations. Recent randomised controlled studies of the outcomes associated with red cell transfusion in surgical or paediatric/neonatal settings have generally indicated that 'less may be better', while several observational studies analysing large surgical databases have suggested that all-cause mortality tends to be worse in transfused patients.

The oft-repeated advice to prescribers to 'balance the risks and the benefits' may be even less useful than we had once hoped.

Keywords Blood donation, blood transfusion, HIV, HTLV, hepatitis B and C, randomised controlled studies of red cell transfusion, transfusion-related infections

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UPDATE IN HAEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background The haematopoietic system is one of the most proliferative organs in the body – producing 2.5 million red cells every second. At the origin of this system is the pluripotent haematopoietic stem cell, capable of differentiating into all blood cells. Haematopoietic stem cell transplantation is used to restore failed bone marrows such as in aplastic anaemia, to facilitate the delivery of high-dose chemo-radiotherapy against malignancies, or to seek to cure malignancies (principally haematological) by completely replacing the patient's own bone marrow system with that from a donor. Autologous transplants use the patient's own stem cells; allogeneic transplants use a donor's stem cells.

The source of stem cells is evolving – previously bone marrow was used, but peripheral blood stem cells are currently the most widely used stem cell source. Cord blood stem cells are a newer development. While sibling donors are the most widely used in allogeneic transplantation, unrelated donors are also a major source for transplants, and there are currently more than 11 million human leukocyte antigen-typed potential donors on registries worldwide. New developments in haematopoietic stem cell transplantation include reduced-intensity conditioning regimens, supplementation of the graft versus leukaemia effect by infusion of donor

lymphocytes, developments in stem cell mobilisation and extending indications for transplantation.

Keywords Allogeneic transplants, aplastic anaemia, autologous transplants, bone marrow, cord blood, haematopoietic stem cell, HLA-typed potential donors

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MULTIPLE MYELOMA

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Background Multiple myeloma is a complex haematological malignancy that is currently incurable. It is associated with significant bone complications which often have a major impact on quality of life. Over a 21-month period, more than 50% of myeloma patients can expect to develop a significant skeletal complication, around 38% will develop pathological fractures, around 34% will require bone radiation, 10% will develop hypercalcaemia and 3% might develop spinal cord compression. This prevalence of skeletal complications has been greatly reduced with the use of bisphosphonate therapy, and pamidronate, clodronate and zoledronate have all been shown to reduce skeletal complications of multiple myeloma.

Recent guidelines have been released on how we should use bisphosphonate therapy, and these will be discussed. The complications of bisphosphonates include GI intolerance, flu-like symptoms, anaemia, scleritis, renal problems and osteonecrosis of the jaw. Newer therapies for multiple myeloma include vertebroplasty and kyphoplasty. In future a better understanding of myelomatous bone disease and the role of secreted factors in achieving a significant imbalance between osteoclasts and osteoblasts may improve our ability to treat and reverse the adverse effects of myelomatous bone disease.

Keywords Bisphosphonate therapy, clodronate, multiple myeloma, pamidronate, zoledronate

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CHRONIC LYMPHOCYTIC LEUKAEMIA – PROGNOSTIC FACTORS AND MANAGEMENT

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Background Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the UK. Our understanding of CLL has increased dramatically over the last five to ten years. Recently described biological prognostic

markers can predict the likelihood that an individual patient will progress to requiring therapy, and can also be used to select the most appropriate treatments for individual patients. In particular, patients with a deletion of the short arm of chromosome 17 (or p53 mutation) have a poor response to conventional chemotherapy and a short survival. Some therapies, such as monoclonal antibodies and high doses of corticosteroids, are effective in a p53 independent manner and can be effective in this high-risk group of patients.

The 'gold standard' chemotherapy for patients with CLL who have no significant co-morbidity is the combination of fludarabine with cyclophosphamide. The addition of monoclonal antibodies to chemotherapy appears to improve the efficacy of therapy. Better remissions, including the eradication of detectable minimal residual disease, are associated with prolonged progression-free and overall survival. The role of consolidation therapy with alemtuzumab (Campath) and that of allogeneic stem cell transplantation are currently being evaluated in CLL.

Conclusions Improved knowledge of the biology of each individual patient's CLL as well as significant advances in the available treatments is leading to a revolution in our approach to the therapy of CLL.

Further reading

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Keywords Alemtuzumab, chronic lymphocytic leukaemia, cyclophosphamide, fludarabine, monoclonal antibodies, prognostic factors

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PARADOXICAL THROMBOCYTOPENIA

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Background Thrombocytopenia is not uncommon in hospitalised patients (12%). When severe (<20–50 × 10⁹/L), it is typically associated with a primary haemostasis bleeding pattern (petechiae, purpura and mucosal bleeding). Occasionally, thrombocytopenia may paradoxically be associated with thrombosis – when

thrombocytopenia is due to increased platelet consumption within clot, rather than due to reduced platelet production or increased platelet destruction. These platelet consumption syndromes are important to recognise as the prognosis and treatments differ.

Methods or theme 'Normal' thrombus is insufficient to cause thrombocytopenia. However, given excessive activation of the coagulation system, thrombocytopenia may result (e.g. disseminated intravascular coagulation). Excessive activation of platelets may result in paradoxical thrombocytopenia without the depletion of coagulation factors. Thrombotic thrombocytopenic purpura is caused by deficiency of the metalloprotease ADAMTS-13 (inherited or autoimmune), which normally prevents the circulation of excessively large von Willebrand factor multimers. These cause platelet-rich thrombi in cerebral and renal vessels. Treatment involves plasma exchange with fresh frozen plasma (replacing ADAMTS-13 and removing any autoantibody).

Another important condition is heparin-induced thrombocytopenia. Antibodies formed to heparin-PF4 complexes bind Fc receptors on platelets, leading to activation, aggregation and thrombus formation (mostly venous). Unrecognised, this condition can be fatal in 30% of cases. Heparin-induced thrombocytopenia is more common in surgical patients and those receiving

unfractionated heparin. Thrombosis is heralded by an unexpected drop in the platelet count ($\geq 50\%$, typically to $20\text{--}100 \times 10^9/\text{L}$) after 5–12 days heparin exposure. Heparin-induced thrombocytopenia is rare beyond 14 days and antibodies are generally short-lived ($\sim 100\text{d}$). The key to successful management is early diagnosis, cessation of all heparin therapy and initiation of an alternative parenteral anticoagulant. Patients with the condition tend not to bleed and do not need platelet transfusion.

Conclusions In patients developing thrombosis despite a low platelet count, always consider the possibility of underlying heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura or disseminated intravascular coagulation.

Further reading

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Keywords Disseminated intravascular coagulation, fresh frozen plasma, heparin, heparin-induced thrombo-cytopenia, metalloprotease ADAMTS-13, thrombo-cytopenia, thrombocytopenic purpura, von Willebrand factor

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