

Haematology

A symposium held on 4 November 2011 at the Royal College of Physicians of Edinburgh

WHAT IS BEST SUPPORTIVE CARE FOR THE ELDERLY MYELODYSPLASIA PATIENT - ARE THERE ANY ALTERNATIVES?

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Myelodysplasia (MDS) patients have a median age of 74 years. Patients with lower risk disease (70% patients) have chronic anaemia and a median survival of 4–11 years, and high-risk MDS has a median survival of <1.5 years. The mainstay of treatment is supportive rather than curative, predominantly with red cell transfusion. Red cell transfusion dependence is an independent adverse prognostic factor for overall survival in low-risk MDS. Cardiovascular morbidity/mortality is high; the relative contributions of chronic anaemia versus complications of red cell transfusion (e.g. iron overload) remain uncertain. In the European Leukemia Net registry of low-risk MDS (n=1000) median pre-transfusion haemoglobin concentration is 8 g/dl indicating that in current practice most patients are significantly anaemic despite red cell transfusion. Quality of life is impaired in MDS, with dyspnoea and fatigue the predominant symptoms and EQ-5D scores lower for transfusion-dependent patients. Active pharmacological therapy may be aimed at improving cytopenias, modifying disease or rarely at disease cure. Erythropoiesis stimulating agents improve anaemia in up to 60% patients if algorithms for high prediction of response are used. Lenalidomide produces red cell transfusion independence in 50–60% low-risk MDS patients with the del(5q) chromosome abnormality. Azacitidine prolongs survival in high-risk MDS patients and red cell transfusion independence in 45%. Curative options include intensive chemotherapy and allogeneic stem cell transplantation but are available only to the small minority.

ANTICOAGULANT BRIDGING

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Vitamin K antagonists (VKA), principally warfarin, are used extensively for the prevention of thromboembolism in patients with atrial fibrillation, and in those with mechanical heart valves and other potential sources of systemic embolism, as well as for the prevention of recurrent venous thromboembolism. Treatment is often continued long-term. The major side-effect of treatment

with VKAs is haemorrhage and the risk is increased by invasive procedures and surgical interventions. Because of the protracted time course for the resolution of the prohaemorrhagic effects of VKAs after their withdrawal, as well as the slow onset of action, substitution of an alternative anticoagulant, usually a heparin, is often considered in order to reduce the risk of thromboembolism and bleeding during and after such procedures and interventions. However, the risk of thromboembolism associated with interruption of VKA treatment varies greatly between patients, largely determined by the indication for anticoagulant therapy. For example the risk is relatively high in a subject with a mitral valve prosthesis who is in atrial fibrillation, and much lower in a patient with atrial fibrillation only. Furthermore, the risks and potential consequences of increased bleeding are procedure dependent, for example they are high for some neurosurgical procedures and low for outpatient dental surgery. In addition, individual patient factors modify the risk of bleeding on heparin, for example renal impairment.

There is a lack of high quality evidence to guide treatment decisions in relation to the need for bridging therapy and the optimal regimens for the full range of indications. Overall, rates of thromboembolism associated with brief interruption of VKA therapy are low, with the possible exception of patients with mechanical heart valves. When bridging therapy with heparin is employed, excessive haemorrhage can usually be avoided if the drug is discontinued 12–24 hours before the intervention and reintroduced only after haemostasis has been secured. Although the rapid reversibility of unfractionated heparin is a potential advantage, the unpredictable response between subjects and the need for laboratory monitoring of unfractionated heparin dosing tend to favour low molecular heparins for use in bridging therapy.

The available data suggest that VKA therapy should not be interrupted for outpatient dental procedures if the INR is <4. The same may apply to some other interventions such as diagnostic coronary angiography, percutaneous coronary interventions and cataract surgery, although the evidence is less robust. In most other situations, the approach to clinical management should be individualised with consideration given to the perceived thromboembolic risk and the risk of bleeding due to heparin therapy. There is a need for more well-designed clinical trials of anticoagulant management, especially in patients with mechanical heart valves.

The introduction into clinical practice of novel oral direct inhibitors of thrombin or factor Xa may simplify the management of planned interventions, as the half-life is short and the onset of action rapid on reintroduction. However the lack of established treatments to immediately reverse their prohaemorrhagic effects may be problematic.

Further reading

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IS WARFARIN DEAD?

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Between September 2009 and September 2011 three mega-trials with new oral anticoagulants for patients with atrial fibrillation to prevent stroke have been published. In addition, for two of the new agents, phase III trials on the treatment of venous thromboembolism the results have been published. Overall, the new agents, dabigatran, rivaroxaban and apixaban, are at least as effective as warfarin and are associated with a significantly reduced risk for intracranial hemorrhage. No routine laboratory monitoring or dose adjustments were needed although renal function should be checked at least annually. In Canada, where dabigatran has been approved for long-term treatment for a year, some, but so far for economic reasons only a small minority of patients, have been switched from warfarin to dabigatran. A higher proportion of anticoagulant-naïve patients have received the new drug.

Warfarin is inexpensive, currently in Canada at a daily cost of 1/30 of dabigatran, but the monitoring costs and thereby related indirect costs are high. Leaving the pecuniary aspect aside, there are several patient and treatment characteristics that would argue for warfarin in certain subsets. A track record of stable prothrombin times (PT) or, conversely, poor compliance; identifiable and adjustable causes for instability of PT; moderate-severe renal failure and gastrointestinal disease may actually be good reasons for using warfarin rather than the new drugs. In addition, patients with mechanical heart valves have not yet entered into any study with the new anticoagulants and should not under any circumstance be prescribed any of those until the effective dose has been determined in appropriate trials.

Warfarin will therefore still be around for another 5–10 years, at least.

MICRO RNAs – WHAT ARE THEY AND WHAT IS THEIR ROLE IN HAEMATOLOGICAL MALIGNANCIES?

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Understanding the regulatory processes that direct specific gene expression is key to our understanding of cellular biology in healthy and disease states. In recent years a new dimension to this regulation has emerged as it has become increasingly clear that non coding RNA molecules play a central role in the regulation of protein synthesis. So called 'microRNAs' are highly conserved through evolution and inhibit translation of specific target mRNA molecules through various different mechanisms. The number of microRNAs identified continues to increase, with over 1,400 human microRNA sequences now annotated on the microRNA database, miRBase (<http://mirbase.org/>).

There has been a huge expansion in our understanding of how microRNA networks are deregulated in a range of malignant and non malignant diseases which may have significant impact on routine clinical practice, particularly in the areas of diagnosis and predicting prognosis. Furthermore, examples are being uncovered where loss of normal microRNA function appears to be causal in terms of disease initiation and propagation, raising the possibility that this could be a potential area for therapeutic targeting. In this overview I shall review our understanding of microRNAs in haematological malignancy.

EPIGENETICS – FROM BASIC SCIENCE TO BEDSIDE APPLICATION

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In the last decade, epigenetic changes have been recognised as major drivers of the malignant phenotype. An epigenetic trait is defined as a stably heritable phenotype that results from changes in a chromosome without an accompanying alteration in the DNA sequence. Epigenetic changes are mainly acquired through DNA methylation or post-translational modifications of histones. Mutations in the *de novo* methyltransferase *DNMT3A*, that catalyses the conversion of cytosine to 5-methylcytosine, are common in acute myeloid leukaemia (AML). The *TET2* gene, which converts 5-methylcytosine to 5-hydroxymethylcytosine, is inactivated in myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), AML and chronic myelomonocytic leukaemia (CMML), while AML cells harbouring isocitrate dehydrogenase 1 and 2 mutations display a hypermethylation phenotype. Interestingly, methylation ‘signatures’ have been shown to correlate with prognosis in large AML cohorts. *MLL1*, one of the most commonly rearranged genes in AML, encodes a histone methyltransferase that methylates histone H3K4. The *EZH2* gene, encoding an H3K27 histone methyltransferase, is inactivated in MDS, MPN and myelofibrosis, while gain-of-function *EZH2* mutations are frequently observed in large B-cell lymphoma. These examples illustrate discoveries in basic science that are driving the development of so-called ‘epigenetic therapies’ in the haematology clinic. In the context of MDS, 5-azacytidine, a DNA hypomethylating agent, is already providing significant survival benefit over conventional care regimens while the histone deacetylase inhibitor Vorinostat is showing efficacy in cutaneous T cell lymphoma. The discovery of novel epigenetic targets in the future will continue to impact significantly on diagnosis, prognosis and treatment in clinical haematological practice.

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AUTOIMMUNE HAEMOLYTIC ANAEMIA

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Autoimmune Haemolytic Anaemia (AIHA) is an uncommon disease caused by antibodies directed against antigens on the red cell surface. It often occurs in association with other conditions, such as chronic lymphocytic leukaemia. The antibodies cause premature red cell destruction, either intravascularly or extravascularly. Diagnosis comes from demonstrating increased red cell turnover and the detection of autoantibodies.

The mainstay of treatment, if necessary, is immunosuppression by corticosteroids. Second line treatments include other conventional immunosuppressive drugs, splenectomy and the monoclonal antibody rituximab. Transfusion support is difficult due to the autoantibody causing ‘positive’ results and a high incidence of alloantibodies. Anti complement antibodies have been shown to have a dramatic effect in inhibiting complement mediated lysis in paroxysmal nocturnal haemoglobinuria and may be useful in rare patients with AIHA, but are very expensive.

INVESTIGATION OF PYREXIA OF UNKNOWN ORIGIN

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Medicine has changed a great deal since Petersdorf first described pyrexia of unknown origin (PUO) as a clinical scenario in 1961. Despite technical advances, there are still plenty of patients with fever whose investigation presents a challenge. I will discuss the difficulties of defining what constitutes PUO. A case will be presented and papers that seek to systematise the approach to PUO will be discussed. Whilst every patient with PUO presents unique difficulties, some principles can be deduced:

- Atypical presentations of common disorders are more likely than rare diseases presenting typically
- Travel, sexual, occupational and animal exposure history is essential, but significance needs to be assessed with reference to ‘denominator frequency’
- Bacterial and viral serology rarely tells you what you have not already guessed
- Malignancy is as likely as infection
- Therapeutic trial of antibiotics rarely indicated
- Trial of steroids is almost never indicated
- Imaging and biopsy are always the most useful steps

Key references

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