Experience of Myeloproliferative Neoplasms Guidelines in the United Kingdom: Perspective and International Context

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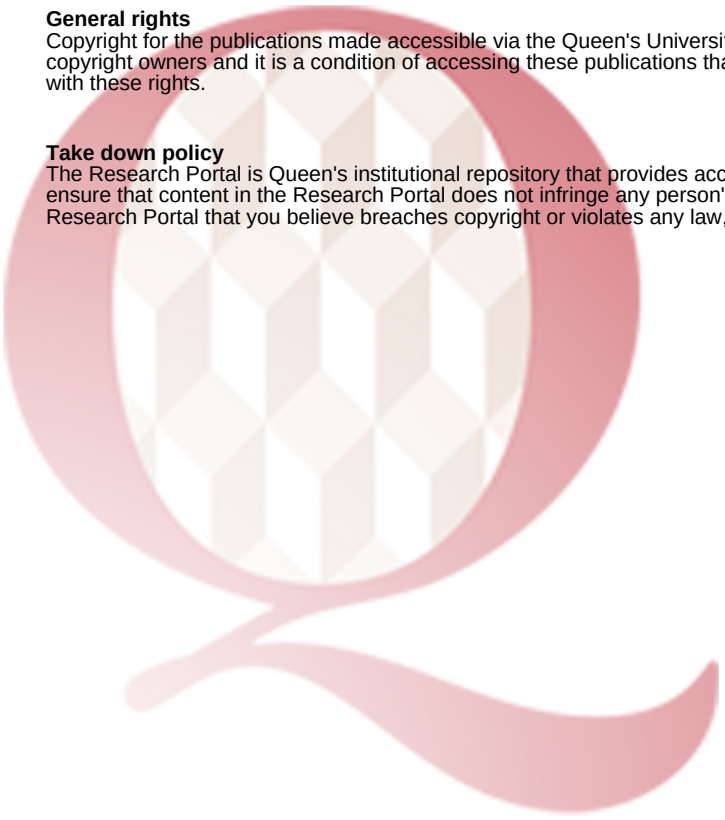

Experience of UK MPN guidelines: Perspective and international context

Running Head: UK MPN guidelines in practice

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Abstract

The UK hematology community has an established process for identifying the need for a guideline, producing and disseminating it. TheBritish Committee for standards in Haematology (BCSH) was formed in 1964with the first published guideline in 1984. . The resultant library of documents includes aspects of laboratory practice in areas such as blood transfusion to highly complex clinical management guidelines. These are published in peer review journals but are also available via a web based platform with free access (http://www.bcshguidelines.com). In this article we discuss the process and history of the production of these guidelines with particular reference to those for myeloproliferative neoplasms.

Introduction

Guidelines are a way of providing a way of providing suggestions for the diagnosis and management of patients. They are usually are usually compiled by those with some expertise in the particular condition. Guidelines may be produced as a statement of opinion from experts but more recently and probably more appropriately those formulating guidelines tend to use methodology to formally assess the evidence of the condition.

The BCSH guideline process

The British Committee for Standards in Haematology (BCSH) was formed in 1964 and worked on standards for laboratory practice. After various negotiations over years BCSH became a subcommittee of the British Society for Haematology (BSH) in 1976. The first published guideline dates to 1984.. BCSH) has been producing guidance for haematologists since that time. These guidelines were initially focussed upon laboratory practice guidelines but subsequently moved into areas of clinical practice over the following years. The primary aim of the BCSH guideline process is to provide haematologists with up-to-date advice on the diagnosis and treatment of haematological disease. The BCSH process or methodology for guideline production has evolved over the subsequent years. Laboratory guidelines were mainly methodologically based but clinical guidelines review literature and access and grade evidence using a standardised process.

Currently there are four BCSH task forces general haematology, haemostasis and thrombosis, blood transfusion and haemato-oncology covering the main areas of haematology practice. Currently guidelines are produced in three different formats. Firstly, evidence-based guidance is produced using a standardised process of conducting systematic review(s) developed following a primary systematic review of the evidence. Secondly evidence–based guideline referencing other previously published evidence-based guideline produced by systematic review for instance international guideline and thirdly guidance and recommendations where there is less robust evidence but for which a degree of consensus is likely to be benifical to patient care.

BCSH guideline writing groups are composed of appropriate experts (consultants or senior healthcare scientists in practice in the UK), a member of the relevant task force and

representative of relevant professional and patient bodies. The members of the writing group are approved by the task force. After formation of the writing group, databases are searched with appropriate keywords, search period and inclusion and exclusion criteria. All references are sourced and evaluated by the group and recommendations formulated. An audit tool is attached to each guideline for assessment of adherence to the guidance. The GRADE nomenclature is currently in use for evaluating evidence and assessing the strength of recommendations[1].

When complete guidelines are reviewed by both the relevent taskforce and then by so-called "sounding boards" which are composed of practising haematologists and provide peer review. When the final guideline is agreed it is posted on the website. The aim is then to publish in a peer reviewed journal, usually the British Journal for Haematology.

BCSH Myeloproliferative Neoplasms Guidelines

The BCSH Myeloproliferative Neoplasm (MPN) guidelines are all evidence based guidelines formulated following primary review of the evidence. When there is a lack of evidence then and expert opinion is agreed. In 2005 the first guideline in MPNs was produced and published. This and all subsequent guidelines in MPNs were developed by various groupings of MPN interested haematologists working in the Myeloproliferative Disorders Study Group which became an official subgroup of the National Cancer Research Institute (NCRI), the NCRI Myeloproliferative Disorders Subgroup in 2006. Experts from other areas were co-opted as required.

The first guideline produced and published in 2005 was a comprehensive guideline on the diagnosis, investigation and management of polycythaemia/erythrocytosis. It covered the diagnostic processes for the investigation of erythrocytosis in detail. The guideline group included expert haematologists and experts from other disciplines including respiratory medicine and paediatric cardiology. The management of Polycythaemia Vera (PV) was included with review of all randomised clinical trials and then recommendations on treatment and cytoreductive therapies were formulated. Management of thrombotic and haemorrhagic complications, pruritus, and pregnancy in PV was also considered. The guideline document then formulated the recommended management of other types of erythrocytosis, apparent erythrocytosis, idiopathic erythrocytosis, high oxygen affinity haemoglobins hypoxic pulmonary disease, cyanotic congenital heart disease and post renal transplant erythrocytosis[2]. As such this guideline, presented advice for a large spectrum of clinical conditions associated with an erythrocytosis. Very soon after the publication of this guideline the acquired *JAK*2 mutation was discovered in many patients with MPN[3] and this had major implications on the diagnostic pathway in PV. This evidence was evaluated and new diagnostic criteria were formulated. This was published as an amendment in 2007 and the website is structured so that this and other amendments are always linked with the original guideline[4].

Following this, thrombocytosis was tackled and in 2010 a guideline for the investigation and management of adults and children presenting with a thrombocytosis was published[5]. This also had a wide remit and covered all aspects of the diagnostic pathway with differential diagnosis. In the management of essential thrombocythaemia (ET) prognosis, risk stratification and thrombotic risk were considered. All therapies were reviewed and treatment specific recommendations made. Management of the specific circumstances, pregnancy, post ET myelofibrosis, leukaemia transformation, children, splanchnic vein thrombosis and surgery were considered. Recommendations were also made for management of reactive thrombocytosis and myelodysplastic /MPN overlap disorders. Following this publication two further articles were published clarifying the diagnostic process. Firstly it was clarified that *BCR-ABL1* testing should be carried out in all patients to ensure a diagnosis of chronic myeloid leukaemia was excluded[6]. The second development was again because of the discovery of new mutations. In the process of evaluating a patient for ET acquired mutations in the *CALR* gene supported the clonal nature of the disorder[7]. This development was incorporated into the diagnostic criteria[8].

The group then considered specifically myelofibrosis and developed a guideline for its diagnosis and management. This also considered the diagnostic pathway and all the management options including myelosuppressive therapy and bone marrow transplantation. Specific clinical situations including splenomegaly and extramedullary haematopoiesis, anaemia and the management of constitutional symptoms were evaluated. Management options for blast crisis, pregnancy and myelofibrosis in childhood were also included[9]. This guideline was published in 2012. Trials of JAK inhibitors were underway at that time and were mentioned in the guideline but the trials had not yet been published. When they were published they needed to be included and management advice modified in view of the trial result. This was published as a modification to the guideline[10].

A comprehensive guideline for the detection of *JAK*2V617F and other mutations was also prepared and published covering laboratory practice including sample issues and laboratory methodology and assay validation [11]. At the present time guidelines for the investigation and management of eosinophilia and a second set of guidelines for the management of mast cell disorders are in preparation.

Thus over an almost 10 years period guidelines for diagnosis and management of all aspects of MPN have been prepared and published primarily aimed at haematology practise in the United Kingdom.

Health Care Utilization

In a digital world, doctors including haematologists in their working environment have instant internet access either by desktop computer or handheld device. The BCSH guidelines are freely available via the BSH website. As such they are instantly available via the internet. In the UK, clinicians consult the guidelines frequently via the internet and often in real time

as part of a consultation. This is evidenced by the fact that there are almost 500,000 page views per year from the UK to the BSH guidelines website in recent years. This is of course a figure for all guidelines. However, the MPN guidelines are always among those which are frequently visited. In 2015, the myelofibrosis guideline and the erythrocytosis guideline were both in the top 10 guidelines visited in the year. This is despite the fact that the erythrocytosis guideline dates back 10 years. In 2014 in conjunction with the British Journal for Haematology an app was prepared of the guidelines. Activity via the app reached a maximum of 9,000 downloads per month in 2015 before starting to decline. In view the costs of maintaining apps this is not being taken forwards.

The guidelines are all published in peer reviewed journals mainly and in the case of MPN guidelines exclusively in the British Journal for Haematology. This journal has universal open access and the guidelines are frequently accessed and downloaded in the UK and beyond from the journal site. The investigation and management of thrombocytosis in adults and children has been one of the most frequently cited and downloaded articles from the journal again reflecting the usefulness of these documents.

In addition to the MPN and other BCSH guidelines being used in day to day clinical practice and sometimes real time during a consultation they are also used in other situations for example as a basis for education both of trainees, for on-going professional development and are accessed by patients and representatives of the pharmaceutical industry alike. Furthermore currently guidelines are also produced with an associated audit tool which facilittates audit and standardisation of practice. Lastly guidelines are also used in the NICE (National Institute of Clinical Excellence) processes at least in part to inform standard practices in the UK and this relates not only to drug reimbursement – the practical example here being the approval of the JAK1/2 inhibitor ruxolitinib but may also relate to approval of funding for specific tests (eg implementation of and funding for molecular tests).

International practice pattern

While BCSH guidelines are written primarily for UK practice and are written in the context of the UK National Health Service they are consulted worldwide. The pattern of downloads for the last 12 months show Ireland (27,085), United States (13,597), India (16,311), Sri Lanka (15,770), Australia (11,553), Saudi Arabia (9.088), Malaysia(8,901), Pakistan (9,138), Italy (11,124) and others (149,880). This shows that the guidelines are widely used in a worldwide context and the MPN guidelines will doubtless have contributed greatly to this activity. For example at the time of writing the modified BCSH guidelines for myelofibrosis incorporate the use of ruxolitinib and were the first widely internationally available MPN guidelines to do so.

Other guidelines do exist for MPN practice the most widely used are those from the ELN[12], and also the ESMO guidelines[13] which are the only other guidelines in the public domain to recommend the JAK inhibitor ruxolitinib. Specifically in the contact of the later therapy the BCSH guidelines, unlike the ESO guidelines for example, suggest practical measures for starting, monitoring and when to stop the therapy all of which are important for rare conditions when clinicians may have little experience of using newer agents.

Changing process

Although the BCSH guideline process has been highly beneficial and successful it is being revised and improved. The scope of searches, with comprehensive inclusion and exclusion criteria for articles are being planned with help from medical writers in carrying out searches after clear questions have been formulated. The National Institute for Clinical Excellence (NICE) has a process for the accreditation of guidelines. While the BCSH has not yet completed a comprehensive process in order to gain accreditation it is working towards implementation of processes in order to gain NICE accreditation.

Under the revised system a new guideline on the diagnosis and management of PV is planned reviewing all the new evidence from trials of new agents in the last 10 years and then formulating evidence based management advice. Review of the evidence for diagnosis and management of secondary erythrocytosis will also be reviewed in the near future. Guidelines for eosinophilia and mastocytosis are in progress.

Conclusions

The well established BCSH process for producing guidelines has evolved since its inception in 1987. For MPN there are 3 existing guidelines for the common philadelphia negative diseases ET, PV and MF these are reviewed and updatedif necessary at least every 3 years or sooner if required due to new findings eg the CALR mutation or new therapies eg the JAK inhibitor ruxolitinib. These are produced using a highly rigorous technique and peer reviewed through the BCSH task forces, a sounding board and then prior to publication in an academic journal. The benefits of such guidelines include: education, standardisation of practice, tool for auditing practice, and on ocassion facilitating reimbursement of novel tests or therapies.

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