

EDITORIAL

Issue Twelve, June 2002

Welcome to the new look PaLMS Info Link. The new format will continue to bring our readers the high quality educational articles they have come to expect from PaLMS. In addition Info Link will contain information relating to the ever changing requirements that continue to impact on health service delivery particularly in relation to pathology.

This issue contains two clinical articles. The first looks at a treatment for chronic myeloid leukaemia. The second is an interesting and timely comparison of ESR & CRP in assessing acute phase response.

The strengthening of the Federal Privacy Act 1988 in December 2001 has impacted on pathology, see page 7. The importance of specimen and patient identification and PaLMS response to these issues can be found on page 8. A new segment called Frequently Asked Pathology Questions or FAPQ appears for the first time also on page 8. Contact information, including collections centres, is conveniently located on the back page.

The editorial team trust you will find the new format to your liking. Please contact us with your feedback or with recommendations for topics you would like covered in future issues.

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A new treatment for chronic myeloid leukaemia using targeted therapy.

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The Haematology department at Royal North Shore Hospital has been involved in a trial of an exciting new treatment for chronic myeloid leukaemia. The drug now known as Glivec, formerly STI 571, is the first of a new class of treatments for malignant disorders. It is a tyrosine kinase inhibitor which blocks the action of a mutant protein known as Bcr-Abl protein within the leukaemic cells. The Bcr-Abl protein is known to be central and crucial for the growth of the leukaemic cells and furthermore is only found in the leukaemic cells but not in normal cells. Hence, if the Bcr-Abl protein could be specifically blocked then it should destroy the leukaemic cells but leave normal cells alone. Studies with Glivec have now been in progress for three years and the results have been spectacular. Chronic myeloid leukaemia has several phases, initially presenting in a chronic phase with a relatively slow progress, it inevitably proceeds to more advanced disease terminating in the acute leukaemia known as the blastic phase. There is often an intermediate phase known as accelerated phase.

The only known cure for chronic myeloid leukaemia has been allogeneic stem cell transplantation in which a donor's stem cells are given to the patient after high dose chemotherapy or radiotherapy. This procedure has a high morbidity and mortality rate and because of this is generally restricted to patients

under the age of about 55 years which means that the majority of patients cannot benefit from this potentially curative therapy.

Interferon with or without additional chemotherapy drugs has been the standard treatment for the last ten years and in approximately 10-20% of patients it can achieve a complete remission of the leukaemia and significantly improve survival. However it seems unlikely that any of these patients are cured of their leukaemia and they need to take the interferon injections for many years. Interferon has significant side effects, particularly fatigue and lethargy, and many patients find it difficult to tolerate. Patients in the accelerated phase and blastic phase of the disease have less therapeutic options and in the blastic phase of the disease even intensive chemotherapy and bone marrow transplantation are rarely successful. The advent of Glivec has now had a profound influence on the management options.

In the chronic phase of the disease, Glivec has been studied in those patients who have failed to respond to interferon. One report of more than 500 patients showed that 90 percent of the patients achieved a major response with normalisation of the blood counts on Glivec therapy. Many of these patients also had improvement in the bone

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marrow chromosome findings with either reduction or complete disappearance of the Philadelphia chromosome which is a hallmark of CML. Complete disappearance of the Philadelphia chromosome and hence remission of the leukaemia is believed to be a predictive factor for long-term survival but it will require long-term follow-up studies to prove if this is truly the case. In the accelerated phase of the disease the response rate to Glivec is again approximately 90 percent but the response unfortunately is not maintained in everybody and after one year approximately 25% of responders have lost the response. Nevertheless this is still a considerable improvement over interferon and other chemotherapy agents. Even in the blastic phase which is the most difficult of all to treat, Glivec still has a major response rate of approximately 60% with many patients achieving complete remission. However once again, like the accelerated phase, the responses are not lasting and after one year most patients have progressed. Interestingly however there is a small proportion (approximately 30%) of patients even in the blastic phase who remain in complete remission at the end of one year.

The side effect profile of Glivec is remarkably good. Most patients either had no side-effects or transient minor side-effects. Serious adverse reactions occur in 1-2 percent of people and include skin rashes, fluid retention, muscle and joint pains, liver toxicity. Most patients who have been treated with interferon comment that the difference in the side effect profile between Glivec and interferon is dramatic. Hence not only is the disease improved but the quality of life is significantly improved in many of these patients. One feature of Glivec therapy that particularly appeals to the patients is the fact that it is given as an

oral capsule (usually 4-6) once a day.

Royal North Shore Hospital haematology department has been the chief investigation site for Glivec studies in New South Wales and we have now treated over 100 patients. This has given us the largest experience with this exciting new drug anywhere in Australia.

The future of strategies such as Glivec in cancer medicine is very exciting. We are now actively involved in developing combination therapy using Glivec plus other treatments known to be effective in CML. It seems likely from laboratory studies that Glivec will enhance the ability of other drugs to attack the leukaemic cells. It may also be possible to combine Glivec with other tyrosine kinase inhibitors or other drugs which act on the chemical pathway within the cell which causes the malignancy. Several such drugs are in development. Importantly, the fact that this type of therapy can work in a particular malignancy gives hope to other research using similar strategies to treat a whole variety of malignant diseases. The unique feature of CML was that we knew the crucial protein which caused the leukaemia. Unfortunately in most malignancies the crucial protein or proteins that cause the malignant changes have not yet been identified. It seems only a matter of time however that the specific defects in each malignancy will be uncovered and this will then pave the way for designing specific therapy to attack each particular malignancy.

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PaLMS Service Centre

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Acute Phase Response – ESR or CRP?

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Acute Phase Response

Tissue damage produces a systemic response that includes fever, neutrophil leukocytosis and an increase in numerous plasma proteins. This inflammatory response, the acute phase response, is mediated by the cytokines interleukin-1 and interleukin-6, which are produced by macrophages at the site of tissue damage. The initiating pathological process may be immunological, infective, ischaemic, malignant or traumatic.

Methods to assess the Acute Phase Response

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the two available methods.

Reasons for Measuring Acute Phase Response

1. Assessing the extent or activity of disease.
2. Detecting intercurrent infection.
3. Monitoring therapy in chronic disease.
4. Predicting outcome.

ESR and CRP should only be measured if there is a reasonable index of suspicion of organic disease and not as a general screening test. The ESR is not a useful screening test in asymptomatic, clinically normal patients. It has a low disease “pick-up” rate of 6 in 10,000. An elevated ESR or CRP does not indicate the cause of the abnormality.

Erythrocyte Sedimentation Rate - ESR

The erythrocyte sedimentation rate is one of the oldest tests in medicine. The Greeks utilised the rate of sedimentation of blood to detect bad “humors”. In the era of modern medicine, the ESR has been used in a variety of settings and fields of medicine. It has been used in an attempt to screen for occult disease, as a “sickness index” and to monitor the course of disease. In more modern times the availability of more specific and sensitive tests means the role of the ESR has become increasingly circumscribed. The evidence that is available suggests that the ESR should only be used in certain circumstances and with an understanding of its limitations.

The physiology of the ESR is well understood. Red cells carry a negative surface charge that impedes red cell aggregation. In the presence of asymmetric high molecular weight proteins, especially those with a positive charge, the tendency for red cells to repel each other is reduced and red cell aggregation is promoted. The major proteins affecting the

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ESR are fibrinogen 55%, alpha 2 macroglobulins 27%, immunoglobulins 11% and albumin 7%. Aggregated red cells sediment more rapidly. In the presence of inflammation, there is a cytokine mediated increase in proteins in the plasma as part of the acute phase response and consequently an increase in the ESR. The ESR is also influenced by red cell factors. A low haematocrit increases the ratio of plasma to red cells and increases the ESR, while red cell changes in iron deficiency and sickle cell disease impede red cell aggregation and result in a lower than expected ESR for a given haematocrit.

The ESR as a screening test is not supported by the literature. The test lacks sensitivity and specificity. It has a poor predictive value. Significant proportions of patients with malignancy or infection have a normal ESR. In the setting of the patient with non specific, unrelated symptoms and signs, a normal ESR is often used as a source of reassurance. However, the low pre test probability of disease in this setting and the lack of sensitivity of the ESR make the value of the ESR in this setting questionable. The presence of a markedly raised ESR, usually indicates pathology of some kind, however, this is usually evident from the clinical details. Another difficulty is the controversy regarding change to the ESR with age. Some studies suggest the ESR rises with age, while some studies looking at the “well elderly” suggest there is no significant change with ageing .

The ESR does have a role in certain clinical situations. In patients with temporal arteritis and polymyalgia rheumatica, the ESR and C-reactive protein are almost always raised. They can be used as an objective measure of response to treatment in conjunction with the clinical response. However, the presence of a normal ESR or C-reactive protein does not exclude the diagnosis. In some connective tissue diseases, e.g. systemic lupus erythematosus, polymyositis, the ESR is more useful than the C-reactive protein for monitoring disease. The confounding effects of anaemia, hypoalbuminaemia and any concomitant acute phase response may limit its usefulness. Similarly a normal or raised ESR does not confirm or refute a diagnosis.

The ESR can be helpful in the context of septic arthritis or synovitis. It is usually elevated. Once again a normal ESR, in a clinically suspicious case does not exclude the diagnosis. In the setting of osteomyelitis, the ESR may initially be normal but usually rises over 24 hours. It is more sensitive than the leucocyte count in this setting.

The ESR is elevated in the presence of a paraprotein. The ESR is of limited value in screening for a plasma cell dyscrasia. However, the confounding effects of anaemia, hypoalbuminaemia and if there is a concomitant acute phase response limit it. A low level paraprotein or light chain disease may be missed by this approach. In cases of severe dysproteinaemia, the presence of marked rouleaux formation with a normal ESR may indicate the presence of a hyperviscosity state.

The ESR is a test that has been used for a variety of purposes over its 70 year history in modern medicine. The current evidence suggests that it has a role in the diagnosis of polymyalgia rheumatica and temporal arteritis. It also has a role in monitoring some patients with connective tissue disorders. In these settings the ESR remains an adjunct to the overall clinical picture. The ESR is of little value as a general screening tool.

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Lower the ESR	Raise the ESR
Haemolytic anaemia	Increased age (controversial)
Hereditary spherocytosis	Infection
Pyruvate kinase deficiency	Inflammation
Sickle cell anaemia	Malignancy
Hereditary hypofibrinogenaemia	Female
Polycythaemia	Pregnancy
Disseminated intravascular coagulation	Diabetes mellitus
High dose salicylates	Hypothyroidism
Corticosteroid	Anaemia
Hyperproteinaemia	Hypoalbuminaemia
Congestive cardiac failure (not in all studies)	Paraprotein
	Connective tissue disease
	Heparin
	Oral contraceptives
	End stage renal failure
	Obesity
	Macrocytosis

*Table 1: Factors that may influence the ESR***C-Reactive Protein - CRP**

C-reactive protein (CRP) is a member of the highly conserved family of proteins termed pentraxins. It is synthesised in the liver and can increase 1000 fold. It is so named because of its ability to precipitate the C-polysacharride fraction from extracts of *Streptococcus pneumoniae*. It has an important anti-inflammatory role, involving removal of proteins, particularly nuclear proteins.

It is the most sensitive and specific acute phase protein for inflammation. The CRP should be used for assessing the degree of inflammation or tissue damage and the response to treatment. It is useful in determining response of infection to antimicrobials.

An increase in C-reactive protein occurs within 6-10 hours after the stimulus and peaks at 48 hours. Following the cessation of tissue damage there is a rapid fall with a half-life of 48 hours. It is the acute phase protein most sensitive to small inflammatory stimuli and in most people, the levels of C-reactive protein are very low and there is only a mild increase with age. It is not influenced by other factors and can be measured on stored serum.

The median normal value of CRP is 0.8mgm/L, and the normal assay measures CRP down to 3mgm/L. There are usually only small increases in CRP in systemic lupus erythematosus, polymyositis, systemic sclerosis, ulcerative colitis and graft versus host disease. The ESR may be more useful in these conditions.

Ultra-sensitive CRP

Measuring very small increases in CRP, within the range of 1-3mgm/L has been considered to be of value in atherosclerosis, osteoarthritis and neonatal infection. There is now an ultra-sensitive method of measuring CRP with the lower level being 0.1 mgm/L.

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Comparison of ESR and CRP

	ESR	CRP
Results affected by:		
Gender	Yes	No
Pregnancy	Yes	No
Level of plasma proteins	Yes	No
Erythrocyte factors	Yes	No
Response to disease process:	Intermediate	Early
Clinical assessment:		
Normal range	Wide	Narrow
Specificity	Moderate	High
Sensitivity	Moderate	High
Reproducibility	Moderate	High

Summary

The CRP is the best method for measuring the acute phase response.
 The CRP is more sensitive, specific and quicker than the ESR.
 The ESR may be more useful in some chronic diseases.
 CRP and ESR should not be used as screening tests in asymptomatic people .

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Privacy in the Health Sector

PaLMS provide pathology services to both the public and private sector therefore have additional responsibilities to those covered by NSW DOH privacy regulations. To reflect those responsibilities the PaLMS Privacy Policy has been developed. The RCPA Guideline on National Privacy Principles is a key reference for the PaLMS Privacy Policy.

Confidentiality of pathology results is important to both you and your patients. In line with NPP 6 to ensure we are only releasing results to those authorised to have access to those results procedures relating to release of results have be modified. In some cases the patient may need to sign a release, once the signed patient release has been received by PaLMS the results can then be forwarded. Copies of the Patient Release form are available from PaLMS Service Centre - 9926 6066 or by visiting the PaLMS website www.palmslab.com.au .

Online access to results via the PaLMS laboratory information system (AUSLAB) is by password protected login only. There is a complete audit trail of who and when the results were accessed. If you have any queries in relation to accessing AUSLAB contact any member of the PaLMS AUSLAB team on 992 67439.

Margaret Hardy

Specimen Labelling

Whilst PaLMS approach to accepting or rejecting a specimen is based on the NATA accreditation requirements it is the safety of our patients that is of primary concern to all PaLMS staff.

In cases where the identification of the specimen is in question often the only solution is to recollect the specimen. To avoid the necessity of recollection and/or delays in processing a specimen it is essential that all specimens are adequately labelled to enable accurate specimen identification. This requires two points of identification eg full name and date of birth. Transfusion have even more stringent requirements, see below. General specimen labelling enquiries should be directed to Gabe Hegedus, Divisional Manager Specimen Logistics on 9926 5530.

Inquest Highlights the Importance of Following Procedures

There have been a series of inquests held following deaths resulting from incompatible blood transfusions in NSW hospitals, both public and private.

The Chief Magistrate has made a series of findings not the least being the need to emphasise to health care providers the need for initial and ongoing education of all health professional staff in regard to procedures and protocols relating the screening and administration of blood products.

Procedures relating to patient and specimen identification play a vital role in patient safety and must be followed. Transfusion related specimen labelling enquiries should be directed to Prof. Robert Flower, Divisional Manager, Transfusion Services on 9926 7745. Fact sheets are available outlining PaLMS requirements. Contact Administration or a member of the Account Management team (8425 3126 or 8425 3127) who will organise for a Fact Sheet to be sent to you.

F A P Q

Frequently Asked Pathology Questions

Q: Why can't I order MBA or Biochem Profile ?

A: The HIC does not recognise either of these abbreviations.

Q: If I want electrolytes, urea, creatinine, urate, liver function tests, calcium, phosphate and magnesium do I have to write out each of these tests in full?

A: In general you should request the specific tests you want. However, if you request C L U E S then PaLMS will perform the above tests.

If you have any FAPQs:

Fax: InfoLink Editor 9926 6395

Email: mkhardy@doh.health.nsw.gov.au

Past Issues

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Laboratory Markers of Bone Metabolism

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For copies of past issue contact:

PaLMS Administration 9926 8086