

MACMILLAN STUDY DAYS AT LANCASTER UNIVERSITY

A central theme in the modern approach to cancer treatment is dissemination of information. Great efforts have gone into producing patient information material and, quite correctly, healthcare professionals spend a lot of time educating patients and their families.

Although specialists are almost overwhelmed by information I think that non-specialists get a raw deal. To improve matters I have been organising study days, each of which has a site-specific or linked group of cancers as a theme. The target audience is non-specialist healthcare professionals – doctors, nurses and any of the professions allied to medicine.

The speakers are experts in their fields who have kindly and freely given their time and the settings have been fairly informal with ample opportunity for questions and discussion. Keeping costs low has been a major concern so that no-one is denied access because they could not afford the course fee.

For each tumour type, the speakers have been asked to cover prevention, diagnosis, epidemiology, specific and supportive treatment including nursing aspects, and outcome. Starting in November 1998 with lung cancer, the days have included gynaecological cancers, haemopoietic malignancies and colorectal cancer. Future plans include head and neck tumours and male cancers.

In November 1999 the third Macmillan Study Day was held at Lancaster University. The theme on this occasion was haemopoietic malignancies and as an experiment the talks were recorded.

All of the speakers succeeded in making the important features and recent developments in their allotted fields accessible to the non-specialist. The intention now is to publish edited transcripts of the talks. Whilst spoken English is very different from written, the editing has been done with the intention of preserving the flavour of the presentations with the speakers' first-hand knowledge and breadth of experience.

The series starts with Guy Lucas, consultant haematologist from Manchester Royal Infirmary. He takes a special interest in chronic myeloid leukaemia and this is the topic he chose.

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CHRONIC GRANULOCYtic LEUKAEMIA

G Lucas, Consultant Haematologist
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Chronic myeloid (or granulocytic) leukaemia (CML) is a chronic myeloproliferative disorder, which comes on slowly and is characterised by overproduction of mature myeloid cells, in particular, neutrophils. There are about 700 cases a year in the UK. Most importantly, the median age is 55. In any consideration of aggressive treatment, therefore, half of the patients would not be suitable, although the younger half will. The only known genuine risk factor for CML is radiation. The disease is often asymptomatic at diagnosis. A patient whom I saw recently was picked up when he came forward to donate blood, and this is not unusual. Quite often patients are diagnosed when they come in for minor surgery. Some patients will have systemic symptoms such as weight loss, bone pain or easy bruising and the physical sign that is particularly associated with this malignancy is splenomegaly.

The laboratory features include a very high white cell count and the cells are predominantly mature neutrophils and neutrophil precursors. The bone marrow is hypercellular and cytogenic analysis of the marrow reveals the Philadelphia chromosome, described in 1971 by Noel and Hungerford.

The normal human cell has 46 chromosomes, 22 pairs and two sex chromosomes (XX or XY). They described an abnormally small chromosome 22. It was later discovered that it had resulted from an unequal exchange of material between chromosomes 22 and 9.

This is the hallmark of CML and it, or its molecular counterpart, is found in virtually all cases. At the molecular level, it turns out that we all have a gene called **bcr** (breakpoint cluster region) on chromosome 22 and one called **abl** on chromosome 9. Although **abl** is an analogue of a gene known to cause leukaemia in chickens, it is actually a housekeeping gene in humans. What happens in CML is that the exchange of material between the two chromosomes has resulted in the production of a chimeric gene. This unusual beast has the head of one gene and the tail of another. The head controls the cells in which the gene is expressed and the tail controls what the gene does. Because this was the first description of a chromosome change associated with a type of leukaemia, and because the molecular details have been worked out, this uncommon malignancy is probably the most

intensively studied cancer in the world. Exactly how this gene leads to leukaemia is fairly well understood now, and speaking broadly, this is a gene which transmits signals from the outside world to the cell nucleus. In a sense, the gene affects where the cell feels comfortable growing within the bone marrow, and how quickly it divides.

CML is a disease which has two phases. In the chronic phase, which is fairly easy to control, the patient will feel well, and if the spleen is large and uncomfortable, it can be shrunk very simply by low intensity treatment. We know, however, that the leukaemia is a time bomb ticking away, and that in most cases it will transform into an acute form which is very hard to treat. If you are going to cure the disease, as opposed to palliate and keep it damped down, the attempt must be made whilst the patient is in the chronic phase. We set ourselves a target, therefore, of trying to carry out definitive treatments, such as a bone marrow transplant, within a year of diagnosis.

Typical chronic phase treatments we use are hydroxyurea and interferon. I see them as palliation in that the patient is kept well for a number of years. Hydroxyurea is taken orally, is well tolerated, and rarely produces unpleasant side effects. I classify this as 'little old lady treatment', suitable for someone who is happy to have simple outpatient treatment which will keep them well for about four years before the disease deteriorates. Interferon is more interesting in that it can have a more profound effect on the disease, but I still see it as something which will prolong the chronic phase and the period during which the patient feels well. But, in fact, interferon does make some people quite unwell, and about 10% find it intolerable, producing insidious malaise and depression.

Treatments which aim to cure the disease, such as bone marrow transplants, or stem cell transplants, are extremely invasive, toxic, and may have many unpleasant side effects. The problem of age comes into this, as does family size. If you put an upper age limit of 55 on the procedure, this immediately excludes half of the patients. With the small families in this country, only about one person in three will have a tissue-matched brother or sister. So already we find that only one in six patients with CML can have this form of treatment. Sibling allogeneic bone marrow transplantation will cure about 60% of such patients, which means that 60% of one in six – ie about one tenth – of CML patients can be cured. Perhaps another 5% will be cured by unrelated donor transplants, but we cannot cure the rest (Figure 1).

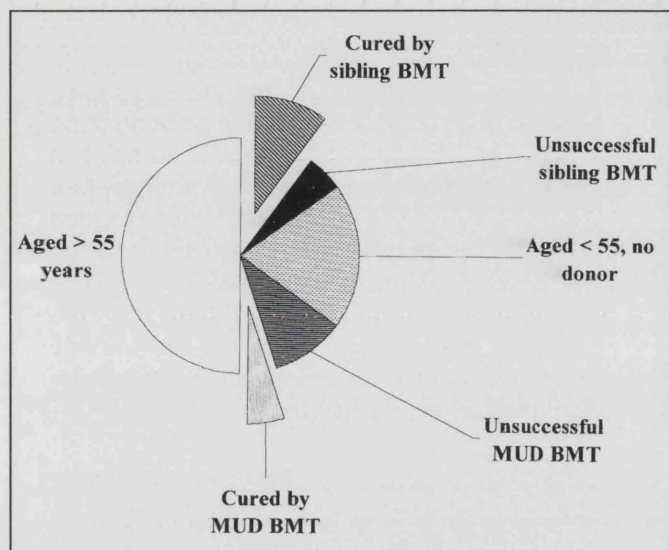


Figure 1 The proportion of patients with CML cured by transplantation (MUD = matched unrelated donor)

If you treat patients with hydroxyurea or interferon there is a steady loss and the survival curve heads down to zero. After a bone marrow transplant, some patients die in the first year, others may relapse later and no patient feels completely well. There is an increased risk of infection, but this steady attrition levels out at about 60% after six years. I tell patients that they exchange early risk for the prospect of a long-term cure, but that they are less well afterwards than they would like to be (Figure 2).

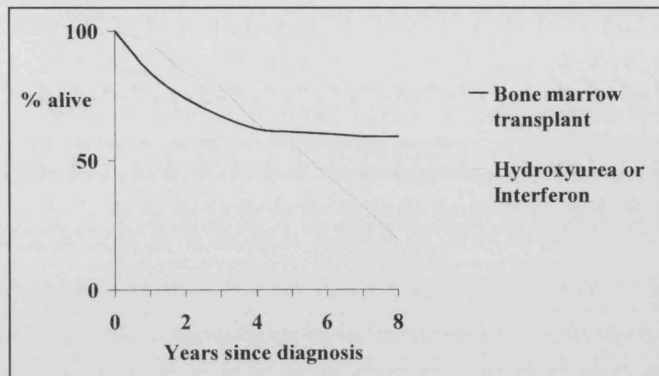


Figure 2 Survival from diagnosis of patients with CML aged <55 years, according to main treatment. International Registry data taken from Gale et al., *Blood* 1998;91:1810

WHAT ARE THE OPTIONS FOR IMPROVING THESE POOR FIGURES?

Firstly, you can increase the numbers of patients having transplants by casting the net wider. It is possible to find unrelated tissue-matched donors for 50-60% of suitable patients from within the UK, and this figure can be increased by searching abroad or using less than perfect matches. At present, we do not really understand how disparate a match still allows a successful transplant.

The other thing we are looking at is making the transplant less toxic, to the point where it becomes largely an outpatient procedure. A recent patient had just such a transplant, and spent only five days in hospital. These less toxic transplants are called 'mini allografts'. If we are to pursue these ways of treating CML, by increasing the number of donors and by reducing the toxicity of transplants, we must have evidence that these measures genuinely prolong survival. Transplantation is an expensive treatment, and consumes a lot of NHS resources. We also need to have better treatment for patients who relapse.

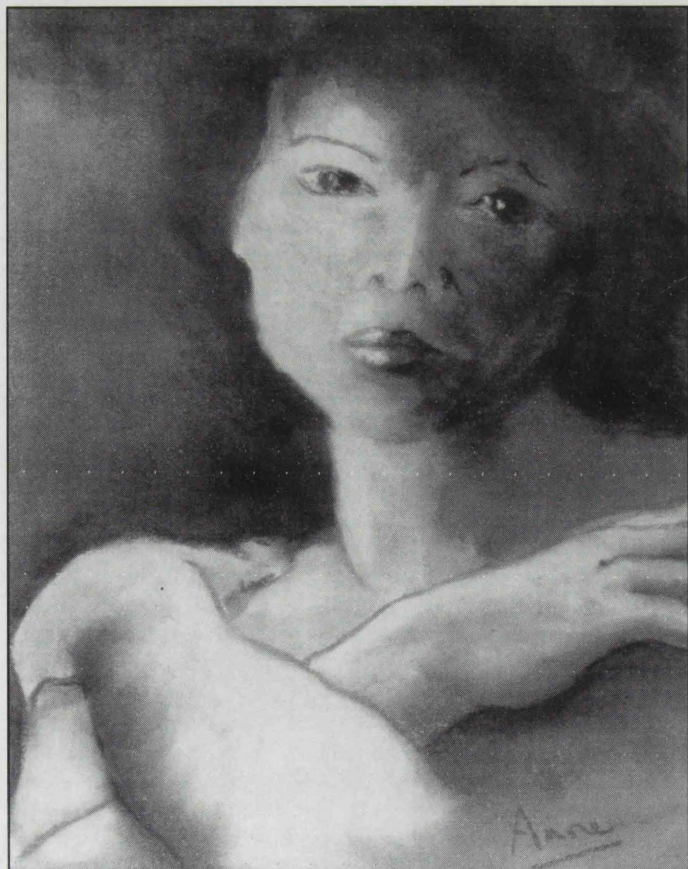
Whilst the obvious donor for any transplant would be an identical twin, it was recognised early on that if you give such a syngeneic transplant to a patient with CML, there is about an 80% chance of leukaemic relapse, which is considerably higher than with a transplant from a well-matched brother or sister. It is not just the chemotherapy and radiotherapy that you are giving to the patient which is curing their leukaemia, there is something about the transplant itself. This is the so-called 'graft versus leukaemia' effect. It seems to be linked to graft-versus-host disease, in which patients become ill as a result of the transplant 'disagreeing' with them.

We have found that in patients who relapse after a marrow transplant for CML, an infusion of peripheral blood lymphocytes from the original donor (the treatment used in the 'Child B' case) will bring about a further remission in 75% of cases. This may, however, be at the cost of causing more graft-versus-host disease. This procedure seems to work

best in CML, although it may have a place in other leukaemias, and it led on to the idea of mini allografts. With this procedure, you are not setting a target of immediate complete eradication of the leukaemia with the transplant, but rather just letting the transplanted marrow take root in the patient and then topping up with the donor lymphocytes to erode away at the leukaemia gradually. Evaluation is continuing, and although the results are promising it is too early to say how effective a procedure this is. Increasing the availability of transplants at less toxicity means that older people will be able to have such treatment: in America such transplants are being carried out on patients in their late 70s.

This intensive approach to treatment may not be the only way forward and basic science may be offering us a different and perhaps better way of doing things. For example, a new drug called STI 571 is on trial at present. This drug has been

designed specifically to inhibit the tyrosine kinase protein that is encoded by the 'new' gene **bcr-abl**. It is well-tolerated by the patients and is taken by mouth. Early results in patients with advanced or refractory CML have been promising and this holds out the hope of making the disease easier to treat, and offers a more rational approach than transplantation. The patients who have tried it so far are those for whom there is little else to offer and it may be that if used earlier in the disease the results would be even better. The first randomised controlled trial of this drug in newly-diagnosed patients with CML has just started but I think it will be another two years or so before we can be certain that this really is an advance. STI 571 and other similar drugs may offer effective treatment for CML to all patients, not just the younger ones, or those fortunate enough to have a donor.



If you have ever wondered what the experience of cancer is like take a look at this painting done by a young girl some months after completing surgery, chemotherapy and radiotherapy for breast cancer. The colour of the clouded background is purple, the same colour as the skin markings defining the radiation field. The body hair has gone. The position of self-protection, the vision of sadness, the tragedy are all there and tell a story with much greater power than words could ever do.

Malcolm McIlmurray