CML, A Paradigm Of Malignancy: New Developments In The Treatment Of Haematological Malignancies

Elizabeth Whittaker, Barbara Sheehy Skeffington and Shaun McCann

Chronic Myeloid Leukaemia (CML) is a myeloproliferative disorder characterised by marked marrow hyperplasia, splenomegaly and abnormal chromosomal findings in the transformed cells. This leukaemia, primarily affecting adults between 25 and 60 years of age, accounts for 15 - 20% of all cases of leukaemia.[1] A markedly elevated leukocyte count is common and the predominant circulating cells are neutrophils and metamyelocytes, with a small number of myeloblasts usually detected in the peripheral blood. It is a clonal proliferation of pluripotent stem cells which predominantly differentiates along the granulocytic pathway.[2] In approximately 90% of patients with CML, the Philadelphia chromosome representing a t(9;22) translocation, is found in all dividing progeny of multipotent stem cells (Figure 1).[3]

Clinically, the initial symptoms may be non-specific, including fatigue, weight loss and weakness. Diagnostic criteria include an elevated white cell count, splenomegaly and presence of the Philadelphia chromosome in the marrow cells. The differential diagnosis includes leukaemoid reactions, polycythaemia vera, myelofibrosis and essential thrombocythaemia. After about 3 years, 50% of the patients enter an "accelerated phase", characterised by increasing anaemia, thrombocytopaenia, and transformation into acute leukaemia (blast crisis). In the remaining 50%, blast crises occur abruptly without an intermediate accelerated phase.[4]

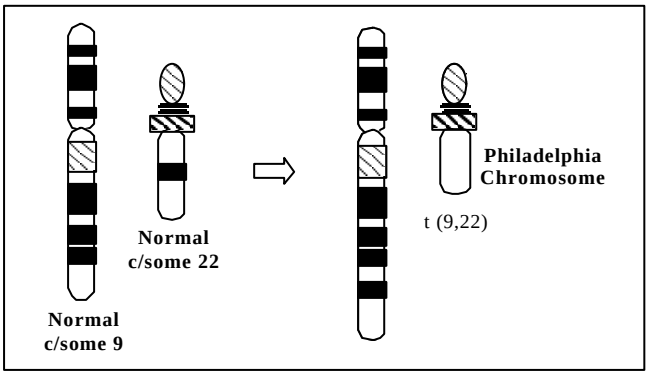

Figure 1: *Reciprocal translocation between chromosomes 9 and 22 to form the "Philadelphia" Chromosome seen in chronic myeloid leukemia.*

Presently remissions are induced with chemotherapy, but the median survival of 3 to 4 years is unaltered. Interferon treatment restores Philadelphia chromosome negative haematopoeisis in a subset of patients.[5] Bone marrow transplant (BMT) is the only curative therapy resulting in long term disease free survival in 75% of cases (Figure 2), but it is limited to patients <55 years who have a matched sibling donor.[4] In the last 5 years the use of matched unrelated donors has gained acceptance but age limitations and toxicity remain limiting factors.

Today, however, molecular biological techniques may revolutionise the approach to therapy for CML. The molecular consequence of the t(9;22) translocation resulting in the Philadelphia chromosome, is the creation of the fusion protein BCR-ABL.[6] The BCR-ABL gene rearrangement primarily produces clonal expansion in CML by blocking apoptosis, or programmed cell death.[7] Cellular expression of BCR-ABL is known to make myeloid cell lines proliferate independent of growth factors. The fusion converts c-ABL, which is a tyrosine kinase (TK), from a tightly regulated, predominantly nuclear protein into an abnormally regulated cytoplasmic TK. Because of the high specific activity and new location in the cell, BCR-ABL gains access to cytoplasmic substrates that the wild-type c-ABL protein might never see, and BCR-ABL can phosphorylate these proteins in an unhindered fashion. Studies of BCR-ABL have identified a number of signal transduction pathways that are activated by this fusion protein (Figure 3). Amongst the signaling molecules involved in these pathways are the GTP binding protein RAS, which links to the MAP kinase cascade, the JAK, and the STAT proteins.[8] BCR-ABL has also been linked to activation of PI3-Kinase.[9]

One consequence of the progress in analysing the molecular and biochemical aspects of BCR-ABL is that this knowledge can be translated into therapeutic strategies that directly aim at BCR-ABL or the signalling pathways that BCR-ABL activates. Based on the fact that BCR-ABL activates so many diverse signal transduction cascades, it would seem

that interfering with a single pathway would be insufficient to block its transforming activity. However, multiple examples have now shown that the malignant transformation by BCR-ABL protein can be blocked by inhibiting a single pathway.

Studies have been performed using farnesyl transferase inhibitors, which block RAS activity and also using Wortmannin which is an inhibitor of PI3-Kinase.[10] Additionally, the effect of tyrosine kinase inhibitors has been investigated. Studies with benzopyranones, benzothiopyranones and tyrphostins have demonstrated only limited potency and selectivity as well as some toxicity. However, the most exciting results have been from studies with the specific tyrosine-kinase inhibitor STI57.[11]

This potent inhibitor of the Abl protein tyrosine kinase was synthesized using the structure of the ATP binding site. STI571 has been shown to be selectively toxic to cells expressing the constitutively active BCR-ABL protein tyrosine kinase. It is also capable of inhibiting both tumour and colony formation of these cell lines. These results were outlined in preclinical studies by Druker *et. al.*[12] Since this study was published in 1996, clinical trials have started with this compound.

STI571 is formulated as a 100 mg capsule and the dosage is 600 mg once daily. In humans it has a half-life of 13-14 hours. To date, the major toxicity is reversible jaundice, with other minor side effects of 'acid indigestion', occasional nausea and vomiting, anaemia, cramps, and joint pains being described. A maximum tolerated dose has not been reached, but no more than 800 mg daily has been given.

The data from phase 1 clinical trials, as presented at the annual meeting of the *American Society of Hematology* 1999 were very promising. The study began in June 1998 and was conducted on 61 IFN-refractory patients. These patients had either displayed no haematological response after 3 months on treatment; no cytogenetic response after 1 year; had a loss of response; or intolerable side effects. There were 11 dose ranges from 25 mg to 600 mg. The median duration of treatment was 190 days with variation from 17-439. Prior to treatment, the median duration of disease was 3.7 years and the median age was 57. The study included 31 patients who received more than 300 mg STI571 per day. Of these, 100% showed a haematogical response, with counts returning to normal within 2-3 weeks; 35% showed a cytogenetic response, with loss of the Philadelphia chromosome, after 2 months, and 45% after 5 months. Only 2 patients took the drug for 8 months and both of these showed a cytogenetic response on 300mg.

In the UK, the first patient to receive STI571 was a multiple-relapse Philadelphia-positive Acute Lymphoblastic Leukaemia (ALL) patient in Newcastle. Since then, 45 patients have enrolled with diagnoses of one of the following leukaemias: chronic phase CML, accelerated phase CML, Ph-positive ALL, Ph-positive Acute Myeloblastic Leukaemia (AML), or CML in blast crisis. There are UK centres in Newcastle, Hammersmith and Nottingham and more are soon to be established.[11] It is hoped that a single centre in Ireland (St. James' Hospital) will coordinate trials under the auspices of the Haematology Association of Ireland.

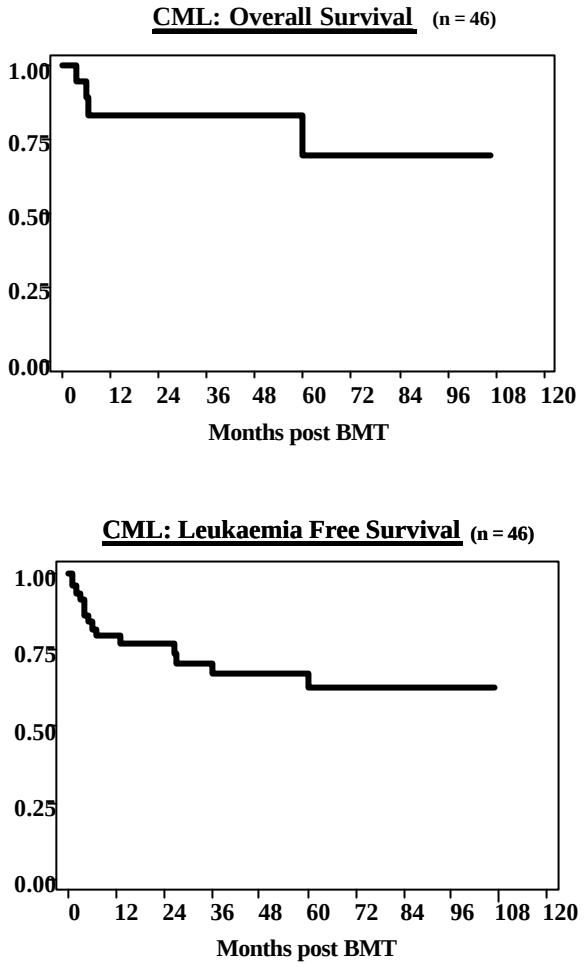

Figure 2: *Kaplan-Meier graphs showing overall survival and leukemia-free survival following bone marrow transplant for CML in first chronic phase in 46 consecutive patients. Recurrence of leukemia can now be successfully treated with a donor lymphocyte infusion improving survival rate, explaining the difference between these two graphs.*

There is much speculation as to whether STI571 should be available to all newly diagnosed patients with CML and some of the arguments for and against are as follows. STI571 is less unpleasant than IFN, but as yet the long-term side effects are unknown. The initial data look very promising, but the durability of responses has yet to be proven. It is unknown whether inducing cytogenetic remission will lead to improved survival prospects. And also it will be difficult to compare IFN and STI571. It is very difficult to find a balance for a trial. It seems that a trial should be done quickly before the drug is widely available making a trial impossible. A randomised study against IFN is not feasible, as patients/doctors may not accept randomisation and patients who have failed on IFN will want STI571 making survival data impossible to interpret. Thus the trial that the CML working group of the MRC (UK) has proposed for all newly diagnosed CML patients is as follows:

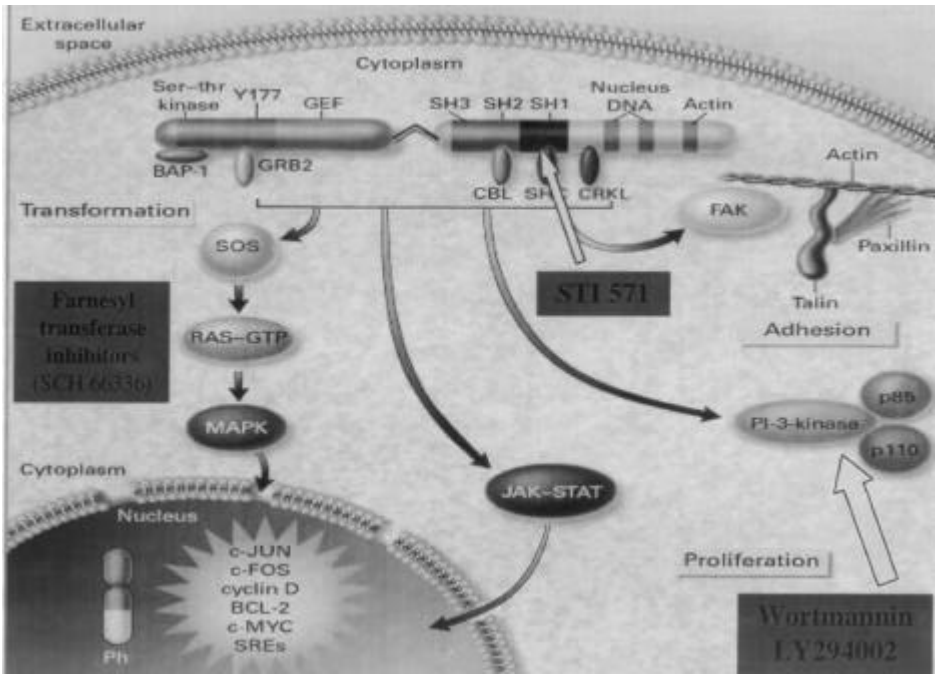

Figure 3: *The signal transduction pathways involved in the action of BCR-ABL and the potential targets for treatment. (Diagram courtesy of S. G. O'Brien, University of Newcastle, from a presentation at a meeting of the Haematology Association of Ireland, February 2000)*

following diagnosis STI571 should be given for 6 months and then the percentage of Ph-positive cells in the bone marrow determined. If less than 30% are Ph-positive then STI571 treatment should be continued and the disease progression monitored. If greater than 30% of the stem cells are Ph-positive at this stage then the patients should be randomized to receive IFN or cytosine arabinoside(Ara-C) alone or autograft followed by IFN/Ara-C treatment. If the patient is less than 40 years old and a donor is available then they should have an allogeneic stem cell transplant and not be recruited to the study. The principal questions addressed by this study are: whether autograft before IFN/Ara-C treatment improves prognosis in patients who do not have a significant cytogenetic response to STI571 at 6 months and what are the haematological/cytogenetic response rates to STI571 in newly diagnosed CML patients?

Is this what the future holds in store for CML patients? These studies are amongst the first to aim at a specific genetic abnormality in human cancer. The results of this trial could change the outcome for haematological malignancies and solid tumours. Success of STI571 in curing CML could pave the way for other specific molecular based treatments of malignancy. Will the dawn of this new millennium see the end of extremely toxic chemotherapeutic regimes for cancer and could it bring hope to all those patients facing an otherwise fatal disease?

Previous claims for "a new cure" have often been disappointing so caution must be exercised. Hopefully on this occasion the preliminary results will be translated into significant therapeutic responses in the long term and will provide the impetus for the development of agents for common cancers.

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