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SPECIAL CONTRIBUTION

Chronic Myeloid Leukaemia
A paradigm for malignancy or just a strange disease?

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الابيضاض النخاعي المزمن
نموذج لورم خبيث أو مجرد مرض غريب؟

شون مكان

الملخص: تحول الابيضاض النخاعي المزمن من مرض مميت إلى مرض يمكن التعامل معه بالأدوية عن طريق الفم. بدأ وصف المرض لأول مرة في منتصف القرن 19، ولم يكن هناك أي علاج مقبول على نطاق واسع حتى ظهور زرع الخلايا الجذعية في أواخر السبعينيات، وكان هذا العلاج ذي قيمة محدودة بسبب المشاكل الناتجة عن قلة المتبرعين والسُمّية. لكن بعد اكتشاف صبغي فيلادلفيا وبعد معرفة مسؤولية النمط الظاهري للمرض الخبيث من قبل المورّث (chimaeric ABL / BCR) فُتحت الأبواب لطرق علاجية أخرى لهذا المرض. تغيرت حياة المرضى المصابين بهذا المرض بعد تطوير مثبطات أنزيم كاينيز التايروسين. وكان العلاج ناجحا جدا مع العديد من المرضى في هَدْأَة المرض السريرية والجزيئية لأكثر من 10 سنوات، بعدها أصبح الامتثال للعلاج مشكلة في الوقت الحالي. تتجه المناقشات في الوقت الراهن نحو الاستخدام المحتمل للجيل الثاني لمثبطات أنزيم كاينيز التايروسين للمرضى الذين شخصوا حديثا لتجنب التكلفة العالية لهذه الأدوية. وعلى الرغم من نجاح مثبطات أنزيم كاينيز التايروسين في علاج الابيضاض النخاعي المزمن ، لم تتحقق مثل هذه النتائج الناجحة في علاج حالات السرطان الشائعة، وبالتالي يطرح السؤال الآتي: هل يُعدّ الابيضاض النخاعي المزمن نموذجا للخبث أو هُوَ مجرّد مرض غريب؟

مفتاح الكلمات: الابيضاض النخاعي المزمن، صبغي فيلادلفيا، مثبطات انزيم كاينيز التايروسين.

ABSTRACT: Chronic myeloid leukaemia (CML), previously a fatal illness, is now readily manageable with oral medication. First described in the 1840s, there was no widely accepted cure until the advent of allogeneic stem cell transplantation in the late 1970s. This treatment was of limited value because of donor availability and toxicity problems. Discovering the Philadelphia chromosome and demonstrating that the BCR-ABL chimaeric gene was responsible for the malignant phenotype opened new avenues. The development of tyrosine kinase inhibitors (TKIs) changed the lives of patients with CML. The treatment has been so successful that compliance is now a problem. Currently under discussion is the possible use of more expensive second generation TKIs for newly diagnosed patients. In spite of the success with TKIs, treatment of common cancers has not been so successful. Is CML therefore a paradigm for malignancy or just a strange disease?

Keywords: Chronic myeloid leukaemia; Philadelphia chromosome; Tyrosine kinase inhibitor.

Chronic myeloid leukaemia (CML) was first described as a distinct entity in 1845. J.H. Bennett described a young man who died with an enormously enlarged spleen, and D. Craigie published a case of disease of the spleen, in which death took place as a consequence of the presence of purulent matter in the blood.[1,2] Both of these cases were published in Edinburgh. According to Barnett and Eaves, a further case was described in 1845 by R. Virchow.[3,4] However what makes CML such an interesting disease is that it is the first human cancer to be associated with a non-random chromosomal abnormality, the Philadelphia chromosome.[5,6] Nowell and Hungerford described the relatively small chromosome 22, which is present in all cases of CML. This was extremely important because, for the first time in humans, doctors and scientists were able to communicate with one another about a disease which had a specific chromosomal marker; in other words, there was a well-defined chromosomal marker which defined the disease.

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Improvements in Technology increased our Understanding of the Pathogenesis of CML

The exploitation of discoveries is often limited by lack of technology. Likewise with CML, it was not until the introduction of banding technology that Rowley demonstrated that the Philadelphia chromosome, instead of a small chromosome 22, was in fact a reciprocal translocation between a part of the long arm of chromosome 9 and the long arm of chromosome 22 [Figure 1].[7] Current diagnostic methods include fluorescent in situ hybridisation (FISH).

Interesting as these findings may have been to scientists, the real question for medical doctors was, 'Could these observations be the key to new treatments?' To put it another way, was the reciprocal translocation an epiphenomenon or was the genetic abnormality the cause of the malignant phenotype? It took some time but eventually a number of scientists demonstrated that this was indeed the case. Using animal models, Daley, among others, clearly demonstrated that the malignant phenotype was caused by the BCR-ABL hybrid gene on chromosome 22.[8] The fusion of the 3' segment of ABL1 to the 5' part of the BCR gene resulting in BCR-ABL1 transcripts gave rise to the production of a P210 protein in 95% of patients and a P190 in the remaining 5%. This should be established at diagnosis as it may be used to measure response to treatment. This hybrid gene expresses a tyrosine kinase (TK) that is constitutively active and influences adhesion of cells to the bone marrow stroma and cell division, and probably most importantly it inhibits apoptosis. These experiments were seminal because they raised the possibility of a completely new approach to treatment.

From the 1970s to the 1990s, there was no adequate chemotherapy for CML, although prognostic scores were developed.[9,10] The average life expectancy was about three years and death was usually a result of accelerated disease, or a 'blast crisis'. Most patients were diagnosed in the first chronic phase (CP) but the disease inevitably progressed to an accelerated phase and blast crisis, simulating acute leukaemia and death. A blast crisis was initially thought to be a form of acute myeloid leukaemia, but the description by Marks *et al.* of the presence of the enzyme terminal deoxynucleotidyl transferase (TdT) in the cells of some patients clearly showed that the acute leukaemic phase could be lymphoid or myeloid.[11] Treatment of 1CP consisted of busulfan, hydroxycarbamide, or recombinant interferon-α. The former two drugs reduced the white cell count and had some impact on symptoms but did little to halt the inexorable

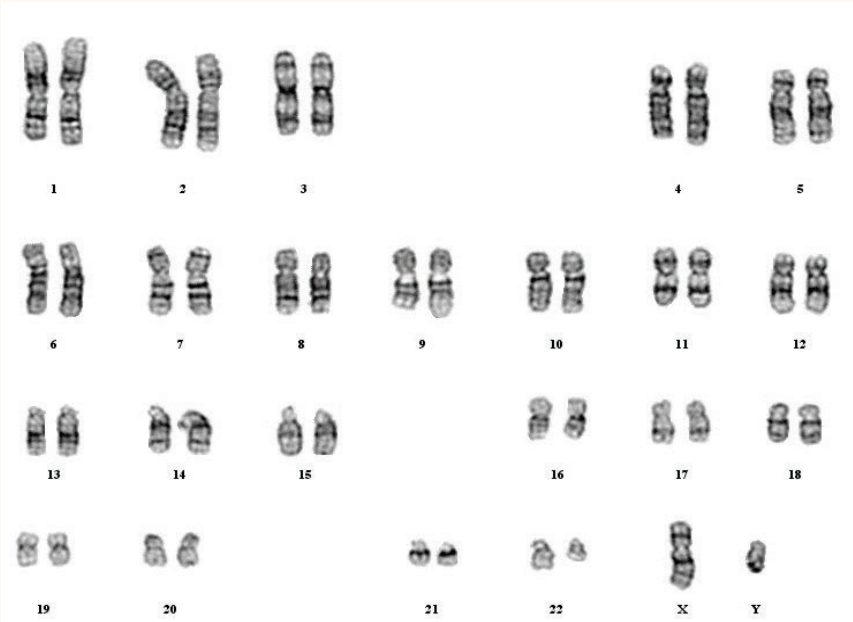

Figure 1: A karyotype showing the Philadelphia chromosome.
McCann S, Foá R, Smith O, Conneally E. Haematology: Clinical Cases Uncovered. Oxford: Wiley-Blackwell, 2009.[36]

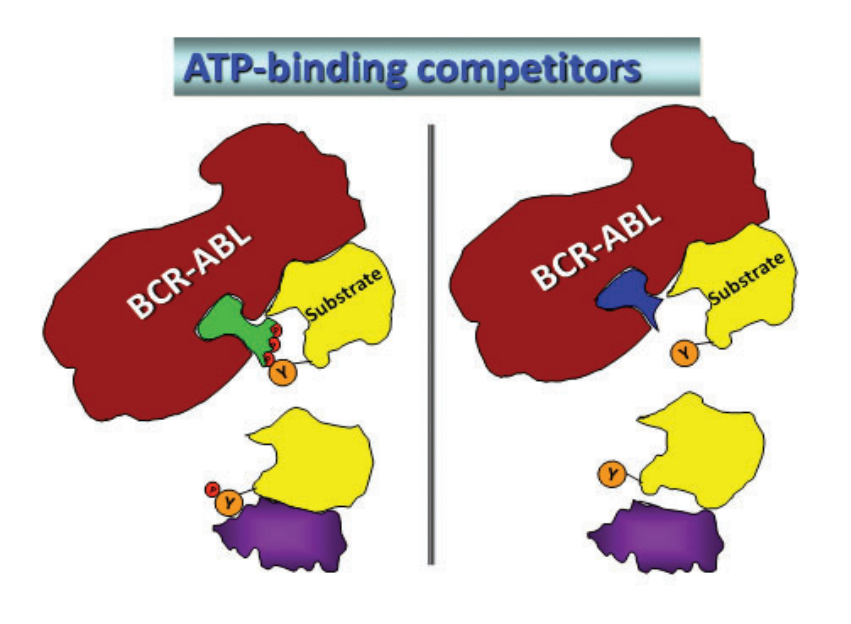

Figure 2: The mechanism of action of tyrosine kinase inhibitors.
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progress of the disease. There was no effect on the underlying chromosomal abnormality. Interferon-α was accompanied by significant toxicity but was occasionally associated with the disappearance of the Philadelphia chromosome.[12] Progression of the disease was associated with genetic instability manifest by +8, +Ph, +19 and i(17q). The only curative therapy before the introduction of TK inhibitors (TKIs) was allogeneic stem cell (mostly bone marrow) transplantation. A number of limiting factors, however, dictated the success of allografting: the availability of a matched sibling donor, expense, and access to an experienced transplant unit.[13] The toxicity of stem cell transplantation is considerable and includes sterility.[14] As the median age for presentation of CML is between 50 and 60 years (depending on the reference), allogeneic stem cell transplantation was not an option for older patients when classical myeloablative conditioning was used. However, despite these limitations, if allogeneic stem cell transplantation was carried out in the first chronic phase within a year of diagnosis, the survival rate was excellent.[15]

The world changed forever with the use of TKIs and the initial publications by Druker *et al*.[16] The first drug that had significant activity against the chromosomal lesion in CML was a TKI known initially as ST-571 (imatinib mesylate) and marketed by Novartis as Glivec®. The important issues for the patients were that the drug was available in an oral form and was relatively free of severe toxicity. This drug launched the term 'targeted therapy' into medicine. Imatinib is a specific inhibitor of the TK domain in the ABL gene (Abelson is a proto-oncogene), c-kit, and platelet-derived growth factor receptor (PDGFR). TKs have an active binding site for adenosine 5'-triphosphate (ATP), which leads to phosphorylation of many intracellular substrates [Figure 2]. Glivec® binds close to the ATP binding site and inhibits the enzyme activity. Inhibition of BCR-ABL by Glivec® also stimulates its transfer into the cell nucleus where it ceases to act as an anti-apoptotic agent.[17] The drug is metabolised by the liver enzyme CYP34A. Toxicity is minimal and consists of anaemia (probably secondary to inhibition of the c-kit), thrombocytopaenia, musculoskeletal pain, and skin rashes. Most patients respond to a single daily dose of 400 mg.

The best-known data demonstrating the efficacy of imatinib come from the International Randomized Study of Interferon and STI571. A seven year follow-up showed a rate of event-free survival (EFS) of 83% and, most importantly, freedom of progression to a blast crisis in 92%. Patients who achieved a complete cytogenetic response (CCyR) at 12 months were less likely to progress to an advanced stage or a blast crisis (97%). Thus, there was a high cytogenetic response rate and that was

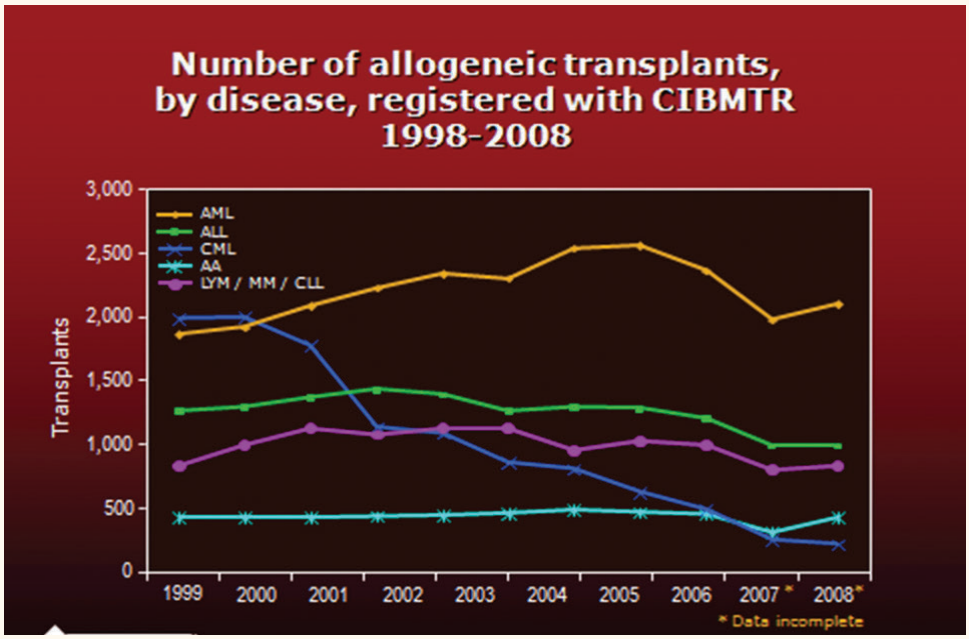

Figure 3: The decrease in numbers of patients referred for allogeneic transplantation.

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AML = Acute Myeloid Leukaemia; ALL = Acute Lymphoblastic Leukaemia; CML = Chronic Myeloid Leukaemia; AA = Aplastic Anaemia; Lym = Lymphoma; MM = Multiple Myeloma; CLL = Chronic Lymphoblastic Leukaemia.

associated with failure of progression of the disease.[18] As well as documenting a cytogenetic response to imatinib, we are now able to apply the most modern technology to monitor patient response using a multiplex polymerase chain reaction (PCR).[19] A three-log reduction in the number of transcripts is now taken as evidence reflecting an optimal patient response. The European LeukemiaNet (ELN) has published criteria for an optimal response to Glivec® and recommendations for other therapies.[20]

Although the outlook has changed dramatically for patients with CML since the advent of imatinib, not all patients respond to this drug, and some patients who respond initially subsequently lose their response. These observations stimulated the development of more potent, second generation TKIs. These drugs are more potent than imatinib, more expensive, and have greater toxicity. However, Druker still gives imatinib to all new patients with CML as an initial therapy.[21] So what is the ideal response to Glivec and who should receive second generation TKIs? The ELN recommendations for an optimal response include a complete cytogenetic response at 12 months and a major molecular response at 18 months.

What should the doctor do if these milestones are not reached? One of the interesting new findings has been poor patient compliance. It may seem strange that a relatively non-toxic oral drug which produces a dramatic effect in most patients would be associated with this problem. Indeed, we know that patients on chronic medication for non-malignant diseases have <50% compliance after 5 years. The incidence may not be as high in CML, but compliance is a problem. The measurement of plasma levels of imatinib was initially believed to overcome this problem as trough levels were shown to be associated with the degree of response.[22] Recent studies from the Hammersmith Hospital in the UK have shown that patients may fail to comply but take an extra dose the day before coming to the clinic, thus making plasma levels an unreliable indicator of compliance.[23] Continual reinforcement of patients with encouragement to take the drug together with a warning of the potential consequences of intermittent therapy should be given. It should also be noted that in a 5-year follow-up, 25% of newly diagnosed patients had discontinued imatinib because of failure to respond, or toxicity.[24]

Another perhaps more serious cause of failure to respond to imatinib or loss of response may be due to mutations in the BCR-ABL kinase domain (ABL1 KD mutations). Techniques to detect these mutations include direct sequencing, denaturing high-performance liquid

chromatography, pyrosequencing, and allele-specific PCR; however, direct sequencing is the recommended technique.[25,26] In some cases, the detection of a specific ABL1 KD mutation will indicate appropriate therapy, whereas many mutations do not carry any prognostic significance. The presence of the T315I mutation is important, as patients with this ABL1 KD mutation will not respond to any of the second generation TKIs, although there is emerging evidence of possible response to an aurora kinase inhibitor, ponatinib.[27–29] If a patient has a suitable donor, s/he should be referred for allogeneic stem cell transplantation. Some mutations are more likely to respond to second line TKIs. ABL1 KD mutations E25K/V, F359C/V, and Y253H seem sensitive to dasatinib, a second generation TKI, whereas F317L and V299L respond to nitolinib.[30]

There are other mechanisms of resistance to imatinib not discussed here, including OCT1 activity and multiple copies of the Ph chromosome. Multidrug resistance polymorphisms may also play a role. In a significant number of patients, the mechanism of resistance to TKIs is still unknown.

What is the place of second-generation TKIs? This is controversial at present.[31] Two recent reports in the New England Journal of Medicine pointed out the efficacy of these agents.[32,33] They both are associated with more rapid and deeper responses than imatinib, but toxicity is increased. Some investigators claim that second-generation TKIs should be used, therefore, for all newly diagnosed patients but, as mentioned earlier, Druker still initiates therapy with imatnib in newly diagnosed patients. The other issue which has become and will be of increasing significance is cost. At present, imatinib costs €30,000 (c. $38,400) per patient per annum and the second-generation drugs are more expensive. As all of these drugs significantly delay the progression of CML, there will be increasing numbers of patients in 1CP. Can patients with a three-log molecular response, which has been maintained for a number of years, discontinue therapy? Unfortunately, the answer is not simple. A number of studies are currently examining this issue but, at present, patients are advised to continue TKIs indefinitely.

What is the current role of allografting? Referring patients for allografting is certainly less frequent than 10 years ago [Figure 3]. The risks associated with allografting, which include chronic graft-versus-host disease (GVHD) and death, far outweigh the risks of taking TKIs, but the expense of taking TKIs indefinitely may be prohibitive in some countries. It should also be remembered that relapse can occur many years after apparently successful allografting. It is clear that imatinib or other TKIs have a role to play in such circumstances.[34,35] Perhaps patients under 25 years of age in CP1 with a fully matched sibling donor should be referred for allografting, but even this is controversial as fatal GVHD may occur in this setting.

In the last 10 years, CML has gone from the most common indication for allogeneic stem cell transplantation to the least common because of the use of effective treatment with TKIs. Whether newly diagnosed patients should be given imatinib or a second-generation TKI as initial therapy remains controversial. Patients who relapse or do not respond to TKIs should be investigated for compliance and/or ABL-KD mutations. Although second-generation TKIs may play some role in the treatment of advanced disease or blast crisis (not discussed here), these clinical entities remain problematical and, if feasible, such patients should be referred for allogeneic transplantation. As mentioned by Druker, one of the benefits of imatinib is that it reduces the chances of a patient progressing to blast crisis and thus makes it difficult to define optimal treatment for advanced disease.[21]

The fact that TKIs may not cure CML but achieve a remission during which the disease remains undetectable at a molecular level seems a philosophical question that is not important for most patients. After all, most diseases, with the exception of infections, remain incurable, but many are treatable. For patients leading a virtually normal life 13 years after the initial diagnosis of CML, and taking TKI medication orally, the issue of undetectable molecular disease may seem somewhat irrelevant.

Unfortunately, the success of the TKIs has not been matched in common cancers such as that of the breast, bowel, or prostate so the question remains to be answered: 'Is CML a paradigm for malignancy, or just a strange disease?'

NOTE

The author wishes to declare that the opinions expressed in this article are his own and do not

necessarily reflect the views of the European Hematology Association.

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