

Controversy surrounding high-cost drug use in oncology

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Although the new anti-cancer drug imatinib has been given NICE approval, it is appropriate to look at why many cancer centres across the country withhold treatment from patients pending implementation of this guidance. The authors suggest that this situation is maintaining the “postcode lottery” that NICE was set up to eliminate

In recent years, a large number of what are considered high-cost anti-cancer drugs have been licensed for use in the United Kingdom. The use of these high-cost drugs impacts severely on the already stretched budgets of health authorities.

The National Institute for Clinical Excellence (NICE) was established to look at technologies where there is genuine uncertainty regarding their value, and to end this uncertainty by providing clear and authoritative guidance for the National Health Service with regard to use and allocation of funding.

The review and allocation of funding often appears to be a long process, time which some cancer patients do not have. Imatinib

(Glivec), for example, was licensed in November 2001 for the treatment of Philadelphia Chromosome Positive chronic myeloid leukaemia (CML) in accelerated phase, blast crisis and in chronic phase following the failure of interferon therapy. At the time of writing, treatment with imatinib is being withheld in many centres across the country, pending implementation of NICE guidance.

This situation is maintaining the “postcode lottery” that NICE was set up to eliminate. Indeed, the Scottish and Northern Ireland authorities have already passed their verdict on imatinib, making it available to all patients within the drug’s current licence.

Evidence for the activity of imatinib in gastrointestinal stromal tumours (GISTs) has also been available for some time. Trusts were notified of the impending GIST indication in December 2001 to enable forward

budgetary planning. The licence for the use of imatinib for c-Kit (a proto-oncogene) positive unresectable and/or metastatic GISTs was granted in June 2002. NICE is not going to set a date to consider imatinib for GIST. Is NICE ever going to catch up? What will happen to patients in the interim?

IMATINIB

Imatinib is a signal transduction inhibitor, one of the first anti-cancer drugs to be developed using rational drug design, based on an understanding of how some cancer cells work.

Imatinib targets the activity of a certain type of enzymes called tyrosine kinases that play an important role within certain cancer cells, ie, c-Kit in GIST and BCR-ABL genes in CML. Imatinib also targets PDGF-R (platelet derived growth factor receptor) and ARG

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gene.

CML

CML has three distinct clinical stages (accelerated, blast and chronic) and imatinib has been studied in each of these stages within phase I and II trials.¹⁻⁵

In May, NICE released a preliminary appraisal consultation document endorsing the use of imatinib only for the accelerated phase of CML. NICE has questioned the degree of evidence available to support use in patients with chronic phase disease who are intolerant to, or are failing to respond to, interferon.

IMATINIB IN CML

In the phase II trial for patients failing to respond to interferon, imatinib achieved complete haematological response in 95 per cent of patients and complete cytogenetic response in 41 per cent.³ (In previous trials of interferon therapy, cytogenetic responses have correlated with improved survival.⁶)

A phase III trial of imatinib for second line treatment in chronic phase disease would be problematical. The historical second line treatment for interferon failures is hydroxyurea. Interferon has already been shown to be more effective than hydroxyurea,⁷ and new data presented at a recent American Society of Clinical Oncology meeting⁸ suggest that imatinib is superior to interferon first line. It may prove difficult to recruit patients into a trial of imatinib versus hydroxyurea when trials have indicated imatinib is more effective than interferon, which is more effective than hydroxyurea.

The IRIS study⁸ greatly strengthens the case for the use of imatinib in chronic phase CML. It is a randomised phase III trial involving 1,106 patients with newly diagnosed CML. The study compared imatinib 400-800mg/day with the gold standard treatment of interferon plus cytarabine. The results from 14 months' (mean) follow up are now available on these patients.

Progression-free survival at 12 months is already significantly better in the imatinib arm (97.2 per cent versus 80.3 per cent, $P=0.001$). This is despite crossover of 39 per cent of the interferon patients on to imatinib (allowed in the study protocol, following lack of/loss of response or intolerance to treatment). Twenty-three per cent of the crossovers from the interferon arm resulted from intolerance to the drug. Intolerance was defined as grade 3-4 non-haematological toxicity, which had to be approved by the Study Management Committee. A combination of this crossover population with those patients who withdrew consent for the study after imatinib was licensed, has meant there are now only 30 per cent of the randomised patients still receiving first line interferon therapy, compared with 90 per cent assigned to imatinib

first line who are still receiving imatinib.

Haematological and cytogenetic response rates in the imatinib arm are impressive. Complete haematological response was seen in 96 per cent of patients (67 per cent for the interferon arm) and a major cytogenetic response was detected in 83 per cent and 20 per cent, respectively, of the imatinib and interferon patients. Sixty-eight per cent of the imatinib responses were defined as complete cytogenetic responses.

The adverse event data from this trial show superficial oedema, rash and muscle cramps to be the only events more common with imatinib than interferon. Rates of grade 3-4 adverse reactions (typically, fatigue, arthralgia and myalgias) were higher in the interferon arm, as expected from the crossover figure.

NICE did not consider these data in support of imatinib for chronic CML after interferon failure and will not be considering its use as a first line treatment until September 2003.

GISTs

GISTs are a group of mesenchymal neoplasms that arise from precursors of the connective tissue cells of the gastrointestinal tract. These tumours are the most common malignant form of sarcoma that arises in the gastrointestinal tract and their incidence is estimated to be 4-6 per million. This type of sarcoma occurs predominantly in middle age and about 70 per cent are found in the stomach.⁹

Historically, GISTs have been difficult to treat because of their high level of resistance to traditional chemotherapy and radiotherapy. For patients with metastatic or unresectable disease, GISTs represented an incurable malignancy with a median survival of approximately 10 to 12 months.¹⁰ Until now, surgery has been the only effective treatment option for most GISTs, with a 10-year survival rate of 30-50 per cent.

IMATINIB IN GIST

Data were recently presented¹¹ from a randomised phase II study involving 147 patients with inoperable or metastatic GISTs who were treated orally with either 400mg or 600mg per day of imatinib. Patients were monitored from one month after initiation of treatment. With a median follow-up of 15 months, the overall rate of partial response was greater than 60 per cent, based on Southwest Oncology Group criteria. At 15-month follow-up, approximately 70 per cent of the patients remained free from treatment failure (ie, there was no worsening of their disease, they had not discontinued treatment or died). The data also show that more than 80 per cent of patients had significant tumour shrinkage or stabilisation of tumour growth; only 12 per cent of patients did not

respond to treatment. To date, the median survival time has not been established.

Most adverse events were mild to moderate in severity and included nausea, diarrhoea, periorbital oedema, muscle cramps, fatigue, headache and skin rash. Twenty-three per cent of patients experienced severe drug-related side effects that included low white blood cell counts, tumour haemorrhage and abdominal pain. Only 13 per cent of patients discontinued imatinib therapy because of intolerable side effects.

The preliminary results of a United States-Finnish multi-centre study ($n=35$) demonstrated that 54 per cent of patients had a partial response to imatinib and a further 34 per cent experienced stable disease. At 10-month follow-up, none of the partial responders had progressed.¹²

A comparable European multi-centre study showed clinical improvement in the majority of patients and ascertained impressive clinical activity of imatinib.¹³

At present, there is no standard of care for patients with unresectable or metastatic GIST. Response rates for true GIST (ie, tumours that express c-Kit) patients to conventional chemotherapy are much lower than for any other sarcomas of non-osseous tissues and range from 0-5 per cent at best.^{14,15}

Imatinib has been designed specifically to target the molecular cause of GIST (c-Kit). The drug is available as oral therapy in a once-a-day dose and, therefore, patients do not have to receive treatment in hospital. Imatinib has been shown to have a superior tolerability and side effect profile compared with conventional chemotherapy or radiotherapy. It has also been shown to provide an improved quality of life compared with standard treatment at any disease stage.

One month's treatment with imatinib at 400mg per day costs approximately £1,500 (usual dose 400-800mg per day). Patients receive treatment until their disease progresses or until the side effects become intolerable.

NICE GUIDANCE

The introduction of NICE has not eliminated "postcode prescribing". Some health authorities use the lack of NICE guidance as a reason to refuse to allocate funding for the treatment involved. Some patients have had to fund their own treatment, as it is the only way that they are able to receive therapy. Alternatively, trusts forgo other cancer resources because of the overspend on drugs. Meanwhile, patients in other regions have their treatment costs covered by the local health authority.

CANCER NETWORKS

Locally, Cancer Networks have been given the task of considering high-cost treat-

ments that have not yet had NICE guidance issued. Although they do not have a budget to allocate resources to fund drug treatment, they have the authority to advise on what treatment should be made available until NICE makes its recommendations. These network decisions may, in theory, perpetuate "postcode prescribing". The way the available evidence is interpreted is rarely influenced by locality. Surely these decisions should be taken nationally?

At a recent meeting hosted by the North London Cancer Network, participants agreed the need for a National Cancer Network drug and therapeutics committee. Although details of the terms of reference for this group are yet to be established, it is hoped that one of its functions will be to prepare consensus statements on new drugs prior to NICE guidance being issued. The group will also help to define where new drugs will fit into current practice.

CONCERNS

Not only are there concerns over the length of the NICE decision-making process, but there have also been questions raised over NICE expertise in interpreting cancer trial data. Oncology trials often have endpoints different from trials in other specialties. This may be due to the patient population, lack of effective comparator drugs or agreement on gold standard treatment. NICE has made requests for phase III data before approving drugs; this is not practicable because of ethical considerations and public awareness of new treatments. Phase II data must often be relied upon in these situations.

Dr Trevor Jones (director general of the Association of the British Pharmaceutical Industry) commented prior to NICE's appraisal of imatinib for CML: "It really is a terrible misjudgement for NICE to fly in the face of expert opinion. NICE has previously said that it cannot recommend the medicine (imatinib) for the early and late stages of the disease (CML) because there is insufficient evidence. However, the medicine is already approved by the Government for use in patients with this distressing form of cancer." NICE appears to be unrealistic in assessing demand for cost-effectiveness data for new oncology drugs. Studies are usually of a limited size and experience is needed in the clinical setting for sufficient data to be accrued. Patients should not be denied a treatment where experts are united on its efficacy. This is currently the situation with imatinib. To complicate the issue further, positive NICE guidance does not release extra money to fund newly appraised drugs. Does this mean that we should be funding the routine clinical use of these drugs while we await NICE guidance? Clinical effectiveness has already been established if a licence has been granted. Health circular

HSC 1999/176 states: "Health authorities and primary care groups and trusts should not wait for guidance from NICE when making budgetary decisions."

RECOMMENDATIONS

For site-specific indications, the use of a particular drug should be agreed on a national level — possibly through a drug and therapeutics committee forum. This way, oncologists, haematologists, oncology pharmacists and other health care professionals from a number of centres could formulate a consensus document.

The NICE decision-making process must be expedited such that, when new drugs are licensed, the NICE guidance is issued concurrently. The current situation is unsatisfactory in that a drug can be granted a product licence, only to find that prescribers cannot use it freely because of a lack of cost-effectiveness data. Even if these recommendations are met, there is still the issue of lack of funding from health authorities (now to be allocated by the primary care trusts). Until this is resolved, many patients will be denied active treatments and we will continue to lag behind the United States and most of Europe in cancer care.

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