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Current Perspective

STI571: a magic bullet?

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1. Introduction

All too infrequently we are confronted with a major breakthrough in the treatment of cancer patients although we have seen important improvements in the approach of the metastastic cancer patients over the last decade.The taxanes and topoisomerase I inhibitors, for instance, represented new drug classes in the field of cytotoxic treatment. However, they did not represent truly novel concepts. More recently, the introduction of monoclonal antibody therapy directed towards specific receptors at the cell surface, such as Rituximab and Herceptin, exemplified a novel means of targeting the cancer cell. On 9 May this year, the Food and Drug Administration in the United States approved the novel drug STI571 (Glivec®, Gleevec®) for use for patients with chronic myeloid leukaemia. This approval marks the start of a new era since STI571 is the first synthetic inhibitor of a signal transduction pathway that has proven to be of benefit for subsets of cancer patients. Recent papers in journals such as the *New England Journal of Medicine* and the *Lancet* further highlighted the landmark that STI571 represents.

2. STI571

Relatively recent molecular biology research has revealed that protein tyrosine kinases (PTKs) play a fundamental role in the transduction of biochemical signals involved in the regulation of cell proliferation, growth and function. Deregulated activity of these enzymes has been observed in a large number of different diseases that include malignant and benign hyperproliferative disorders. Inhibitors of these PTKs could be useful in increasing our understanding of the role of these enzymes and their associated signal transduction pathways in specific diseases, but could also be of crucial importance in the development of new treatments.

PTKs can be divided into subgroups that share similarity in their structural organisation and sequencing within the kinase domain. They can be located either intracellularly (e.g. Abl) or they can be be associated with the cell membrane as receptors for extracellular ligands, (e.g. platelet-derived growth factor receptor (PDGF-R) and KIT)), the receptor tyrosine kinases (RTKs). STI571 (Glivec®, Gleevec®) is a small molecule that is highly selective inhibitor of the protein tyrosine kinase family comprising Abl (the chimeric Bcr–Abl fusion protein found in certain leukaemias such as chronic myeloid leukaemia (CML)), the platelet derived growth factor (PDGF) receptor α and β and the product of the *C-kit* proto-oncogene (KIT) [1–4].

3. STI571 in chronic myeloid leukaemia

The *v-abl* oncogene, originally isolated from the genome of the Abelson murine leukaemia virus [5] encodes a transforming protein with specific tyrosine kinase activity. This transformed product of the human proto-oncogene *c-abl* (the human equivalent of *v-abl*) may play a role in the pathogenesis of several human leukaemias. Chronic myeloid leukaemia (CML) is a haematological stem cell disorder characterised by excessive myeloid proliferation [6]. The Philadelphia chromosome, present in 95% of patients, is the hallmark of CML [7]. The Philadelphia chromosome is formed by a reciprocal translocation between chromosomes 9 and 22, replacing the first exon of *c-abl* with sequences from the *bcr* gene and resulting in a bcr–abl fusion protein that has enhanced tyrosine kinase activity [8]. Expres-

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sion of bcr–abl can induce a disease in mice resembling CML, which provides further evidence that the BCR–Abl protein is a major factor in the pathophysiology of CML. Because of these findings, an inhibitor of the BCR–Abl tyrosine kinase would be expected to have potential as effective and selective treatment for CML.

As stated above, STI571 was shown to inhibit bcr–abl and *in vitro* as well as *in vivo* studies in models provided evidence for drug-induced tumour growth inhibition. Recent important papers published in the *New England Journal of Medicine* [9,10] confirmed the major clinical activity of STI571 in the chronic phase of CML and, to a somewhat lesser extent, in the blast crisis of CML and in Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL). The first study [9] was a phase I dose-escalating study of STI571 performed in 83 patients. 70 failed interferon alpha treatment, 37 of whom had a haematological resistance or relapse and 33 a cytogenetic relapse. 13 patients could not tolerate interferon alpha treatment. Their median duration of having CML was 3.8 years. Patients were successively assigned doses ranging from 25 to 1000 mg/day. STI571 was generally well tolerated and in fact a maximal tolerated dose was not identified. Side-effects consisted of nausea, vomiting, myalgia, oedema, diarrhoea, fatigue and rash. Incidental myelosuppression was also noted. In the vast majority of cases, the side-effects were mild to moderate and only rarely were they severe. Why higher doses were not explored is not indicated in this paper. Importantly, haematological responses occurred in all patients treated with doses of 140 mg/day or greater. Of the patients treated with doses of 300 mg/day or greater, 53 of 54 had a complete haematological response. In addition, 29 of the 45 patients treated with doses of $\geqslant$300 mg had a major or minor cytogenetic response. The most recent information presented at scientific meetings is that these responses seem to be durable, but obviously further confirmation is needed.

A second dose-escalating study [10] assessed antitumour activity in 38 patients with myeloid blast crisis and 10 each with either lymphoid blast crisis or Philadelphia chromosome ALL. They were given doses ranging from 300 to 1000 mg/day. Side-effects were similar to those previously mentioned. 14 of 20 patients with lymphoid blast crisis or ALL had a response including four complete responses. Unfortunately, all but 1 of the responding patients relapsed after a median time of 58 days, indicating that the responses in myeloid blast crisis and ALL are of relatively short duration, in contrast to the data from patients in the plateau phase of CML.

4. STI571 in gastrointestinal stromal tumours

The KIT protein is the RTK for the ligand stem cell factor and is found on a variety of cell types, involving normal as well as tumour cells. Its role in proliferation, development and function of myeloid, germ and mast cells and melanocytes has been established [11]. Deregulation of SCF receptor signalling has been suggested to be involved in a variety of human cancers, including gastrointestinal stromal tumours (GIST), small-cell lung cancer, glioblastoma and prostatic cancer.

GISTs are the most common mesenchymal tumour in the gastrointestinal tract. These tumours are thought to originate from the same precursor as the interstitial cells of Cajal, which are considered to be the pacemaker cells for the autonomous movement of the gastrointestinal tract, i.e. peristalsis [12]. In GIST, mutations in *c-kit* have been reported, resulting in ligand-independent constitutive activation of the RTK [13,14]. In addition, it was reported that STI 171 inhibited phosphorylation of both wild-type and mutant KIT receptors containing a mutation in exon 11, which codes for the juxtamembrane portion of the receptor, but not in cases with a mutation in exon 17, which encodes the kinase domain. Growth of cell lines expressing these wild-type and certain mutant RTKs was also inhibited, which led to studies on STI571 in GIST.

A case report [15] showing major tumour regression with STI571 in a GIST patient previously failing treatments including doxorubicin, ifosfamide, dacarbazine and thalidomide further prompted clinical investigations in this disease entity. Two important studies were recently reported, one in the *Lancet* and one currently only in abstract format [16]. In a phase I study, the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group [16] entered a total of 40 patients with GIST and other soft tissue tumours. Most patients had previously had chemotherapy which had proven to be ineffective. 36 patients had GIST, 4 had other sarcoma subtypes, 2 of which were KIT-positive. The EORTC study identified a formal maximum tolerable dose of STI571 in this patient population. At the dose of 1000 mg/day, dose-limiting gastrointestinal side-effects were noted consisting of intractable nausea, vomiting and diarrhoea. The dose of 800 mg/day, given in split doses of 400 mg twice daily (B.I.D.), was determined as an acceptable dose for further studies. Apart from the side-effects listed as dose-limiting, the investigators also reported rash, oedema, periorbital oedema and other even more infrequent side-effects, most of which were mild to moderate and easily manageable. Myelosuppression was rare, but sometimes severe. From the safety aspect, this study confirms the previously mentioned studies in CML and ALL [9,10]. Importantly, in the 36 patients with GIST patients entered into the study, the objective regression rate was 69% and only 11% of patients progressed. Of those patients that had symptoms from their disease before starting treatment, 89% experienced total relief from symptoms or major symptom improvement. Some

of these symptomatic patients experienced a dramatic and almost immediate effect. Importantly, it seems possible to predict response to treatment within a few days by performing fluorodeoxyglucose-positron emission tomography (FDG-PET) scans pretreatment and a week after the start of treatment. A decrease in uptake of FDG correlated closely with objective response assessment, even though the objective response sometimes occurred weeks to months later. The investigators indicate that in a very small subset of patients, a dramatic increase in tumour size was noted resulting in permanent discontinuation of treatment. Whether this is related to an immediate and extensive inflammatory reaction or a true induction of tumour growth is as yet unknown. It remains possible that patients with different mutations of the KIT receptor show a different response to treatment. This is actually confirmed by the early analysis of the second study which involved a randomised comparison between a dose of 400 and 600 mg/day in GIST patients. At the plenary session of the 21st Conference of the American Society of Clinical Oncology, Blanke and colleagues [16] reported similar response rates in close to 90 patients to that reported for the EORTC study, but in patients with a mutation of exon 9 or 17 or wild-type c-KIT, the response rate was only 20% or less. The side-effect profile reported in the study was similar to that reported in the EORTC study in GIST and the leukaemia studies. Although the study was not powered to detect such a difference, the response rates in the first analysis, as reported at the meeting, might suggest a dose–response relationship and stresses the need for further phase III studies investigating this aspect. At the ASCO meeting, it was indicated that worldwide there are currently large randomised similar studies ongoing comparing 400 mg/day with 800 mg/day (given as 400 mg B.I.D.). While GISTs are relatively rare tumours, it is remarkable that both studies should accrue at such a high rate. Further outcome of these studies is obviously awaited, but in patients with GISTs, certainly those with metastases, for which there is no alternative treatment, the indicated objective and subjective response rates cannot simply be ignored. Patients with GIST should have access to this drug as soon as possible.

5. Current and future perspective

Clearly, the results reported represent a major breakthrough in the treatment of both CML and GIST. The clinical benefit to patients is obvious. For CML, these results should lead to investigations using STI571 even earlier in the treatment, and long-term results will tell us how durable the responses will prove to be. For GIST patients, there is currently no effective treatment at all once radical surgery is no longer an option. The fact that these frequently symptomatic patients can now be adequately treated with an oral drug that has limited side-effects is almost unprecedented. Most patients experience only mild or moderate side-effects, if at all, and those that occur can mostly be easily managed. However, occasional severe side-effects have been reported and are a reason for caution. A kind of tumour lysis syndrome seems to be occurring in GIST in a minority of patients and the consequences are that intensive supportive treatment may be indicated. Most side-effects occur early on in the treatment. At later stages of treatment they seem to decrease or even disappear. Data on long-term treatment with STI571 are currently still lacking, so cumulative toxicity cannot yet be fully excluded.

Importantly, STI571 is the first of a new class of agents to be registered. The synthetic inhibitors of signal transduction have yielded major interest over recent years and now the validity of the concept is proven in clinical studies. Whether STI571 truly represents a magic bullet for GIST, and for the other diseases expressing the proteins targeted by the drug, obviously remains to be seen.

With the first patients going on trial in 1998 and registration for the treatment of CML becoming effective in May 2001, STI571 is certainly the anticancer drug with the shortest period of clinical development. This shows that truly effective agents will prove their benefit rapidly. The downside of the success is the fact the once the news has spread, every single patient will wish to have access to the drug. This carries the risk of uncontrolled use at a time when the safety profile has only been assessed in a relatively limited number of patients. In addition, the pressure of patients and their physicians creates a challenge as regards the drug supply, at a stage when this was not yet really foreseen.

In our opinion, STI571 is one of the most important agents recently developed and certainly the first of a new class to be registered. Since clinical experience is still relatively minimal, patients with STI571-sensitive diseases should still be treated in clinical trials until further experience has been acquired.

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