PERGAMON

European Journal of Cancer Vol. 38 Suppl. 5 (2002) S66–S69

European Journal of Cancer

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Overview of issues related to imatinib therapy of advanced gastrointestinal stromal tumors: a discussion among the experts

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Abstract

Information regarding the activity of imatinib in patients with metastatic gastrointestinal stromal tumors (GISTs) has accumulated rapidly. Nevertheless, several important issues about imatinib therapy as well as these tumors themselves remain to be answered. Importantly, the optimal dose and duration of imatinib therapy are unknown, with daily doses of 400 mg and 600 mg producing comparable response rates in a phase II study. Moreover, the role of surgery following maximal responses to imatinib and those of functional imaging and use of biopsies in monitoring treatment responses need to be investigated. Further understanding of the molecular and pathologic characteristics of GISTs that are responsive or resistant to imatinib is also needed. This paper summarizes a symposium that was held in Helsinki, Finland, in September 2001.

Keywords: Astrointestinal stromal tumor; Muscle-tissue neoplasm; Imatinib mesylate; Receptor protein-tyrosine kinase; Enzyme inhibitor; Proto-oncogene protein *KIT*

1. Introduction

Information about the activity of imatinib (Glivec®, formerly STI571, Novartis Pharma AG, Basel, Switzerland) in advanced gastrointestinal stromal tumors (GISTs) has accumulated rapidly, but it is important to recognize that many issues still need to be addressed (Table 1). These issues are not unique to imatinib, and molecularly targeted therapies that follow in the footsteps of this novel drug will face the same ones. These issues are relevant to the management of patients participating in ongoing clinical trials as well as those being treated outside of such studies. Although sufficient data is not yet available to resolve all issues at the present time, a consensus can be offered concerning how patients with advanced GISTs should be managed during imatinib therapy. This paper summarizes a symposium that was held in Helsinki, Finland, in September 2001.

2. Question: How can we come to a definitive diagnosis of GIST?

GISTs, the most common mesenchymal tumors of the gastrointestinal tract, are usually found in the stomach or small intestine [1]. They are immunohistochemically positive for the stem cell factor receptor Kit (CD117), the product of the *KIT* proto-oncogene, and about 70% of the tumors are also positive for CD34. Approximately 30% of GISTs are positive for smooth muscle actin, whereas a large majority are negative for S100 protein or desmin. Malignant GISTs often express activating mutations of *KIT*, leading to constitutive tyrosine phosphorylation and intracellular signaling [2–4]. In some cases, however, tumors are not positive for Kit, yet they are similar to GISTs in location and clinical features [1,5]. These tumors are

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0959-8049/02/$ – see front matter

Table 1
Issues concerning the treatment of GISTs

- Role of central pathology review in the diagnosis of GISTs
- Relationship of Kit–negative tumors to GISTs
- Identification of patients requiring aggressive therapy following initial surgery
- Selection of optimal dose and duration of imatinib therapy
- Role of surgery following maximal responses to imatinib
- Role of functional imaging and biopsy in monitoring treatment responses
- Identification of molecular and pathological lesions responding to imatinib
- Use of molecular techniques to evaluate presence of minimal-residual disease
- Identification of animal model of GISTs and (molecularly) related tumors

generally undifferentiated and lack other cell-type markers used in the differential diagnosis of GISTs. It remains to be determined whether these "null phenotype" tumors are related to GISTs and whether they should be managed in the same way. Perhaps of greater importance is the need to determine whether a line can be drawn within the population of GIST patients, defining those who do and do not require aggressive therapy following initial surgical resection. Histologic criteria do not provide unambiguous predictive power, although greater tumor size and mitotic activity are associated with more aggressive tumor behavior and poorer survival [6,7]. However, a tumor found in the small intestine is more likely to metastasize than one located in the stomach even if it is of small size and has a relatively low mitotic index [1,8].

The diagnosis of GISTs may be problematic for general hospital pathologists, because they see only a small number of these tumors each year. With imatinib emerging as a viable treatment option, it has become even more important that an appropriate diagnosis be made expeditiously [8]. The analysis of GISTs is often executed differently at various hospitals and laboratories, with non-standardized reagents and methodologies used in some centers leading to inaccurate diagnoses. In study 2222, the rate of false negatives was less than 1%, suggesting that the method used provided a reliable diagnosis of GIST across the different centers in the U.S. and Finland. The methodology utilized in all of these cases required a microscopic inspection of the hematoxylin and eosin stained slide prepared from a paraffin embedded specimen for histopathological identification of GIST based on well-defined criteria [1,5,6]. Additional slides prepared from the same paraffin block are stained using standard immunohistochemical methods and commercially available antibodies and reagents. It should be noted that it is important to carefully retitrate each new batch of the most widely used polyclonal Kit antibodies (using appropriate positive and negative controls). Stromal mast cells almost invariably also serve as a valuable internal positive control. Evaluation of appropriately stained slides reveal that most GISTs show unequivocal diffuse, strong, cytoplasmic positivity [9]. Accordingly, large hospitals should make arrangements for immunohistochemical testing for Kit as part of their high-quality surgical pathology. A central pathology review at expert centers can be justified to help pathologists in different hospitals to learn exactly how to examine these tumors [10].

3. Question: What is the current thinking about the optimal dose of imatinib?

Imatinib produced similar response rates when administered at doses of 400 mg or 600 mg daily in an open-label randomized phase II study which accrued a total of 147 patients with unresectable or metastatic GISTs [11,12], although this study was not large enough to detect a difference between these doses. Overall, 79 patients (53.7%) had a partial response. Although 20 patients (13.6%) have relapsed, the median time to relapse has not been reached [12]. These results show that imatinib is active in patients with advanced GIST. Additional information about the optimal dose and duration of therapy await results of ongoing phase III studies [13,14].

However, at present, some investigators advocate starting imatinib treatment at a daily dose of 800 mg based on a phase I dose escalation study, providing it is tolerated [15]. Side effects after 3 months of treatment with 800 mg are acceptable in some patients, suggesting that normal tissues are not always adversely affected by exposure to relatively high concentrations of the drug. Patients who are responding on the lower doses of imatinib should continue such treatment, but if they stop responding, then the dose of imatinib may be increased, first to 600 mg and, if tolerated, to 800 mg. In a small number of cases, patients who failed on the 400-mg dose either respond or stabilize on the 800-mg dose.

A starting dose of 400 mg may be more appropriate for some patients, particularly those of smaller size with cachexia, poor performance status and a large disease burden. Such patients can quickly develop edema or a fluid compartmentalization during imatinib therapy and then clinically deteriorate. A study of these patients should be considered in which imatinib would be started at an even lower dose, with a goal of escalating to 400 mg daily. However, as the imatinib experience becomes integrated into clinical practice, the rigorous follow-up of patients following initial surgery for GIST will likely become the standard rather than the exception. Accordingly, it is to be expected that most patients with metastatic disease will be detected with smaller and fewer metastatic lesions, whereas those with bulky disease who are at increased risk of this compartmental syndrome will rarely be seen in clinical practice in the future.

It should be recognized that patients taking imatinib

have been communicating via the internet about their experiences. Patients in the U.S. have conducted their own survey of the randomized clinical trial. It will be interesting to ascertain how the subjective measures of this survey compare with the objective measures of the clinical trial, because patient-reported quality-of-life data often differs from quality-of-life data reported by physicians. Because of the concern about toxicity, patients have been pushing to receive the lowest effective dose. The selection of the 400-mg dose for treatment of GISTs was based on several factors, notably the results of the phase I study in chronic myeloid leukemia (CML) patients, and the results from a pharmacokinetic analysis for inhibition of the key tyrosine kinase target [16,17]. In CML, complete hematologic responses were achieved by almost all patients treated with imatinib at doses of 300 mg daily or higher [16]. Although the 300-mg dose may be considered to be the lowest effective dose, at least in CML, a high level of interpatient variability of plasma drug levels has been seen. Thus, the 400-mg dose was recommended in order to provide a sufficient margin of efficacy and minimize any risk of underdosing patients. It should again be noted that information relating actual exposure to imatinib with subsequent clinical outcome is not yet available in patients with GISTs.

Many patients with advanced GISTs typically have large liver metastases at the start of imatinib therapy. As these metastases shrink, the metabolism of imatinib in the liver may be expected to become more efficient. Consistent with this expectation, patients appear to have fewer side effects during long-term therapy. Nevertheless, it remains to be determined whether the pharmacokinetics of imatinib change after 1 year of therapy or in association with a reduction in the size of liver metastases. In the future, surrogate markers may be helpful in selecting the imatinib dose. For example, in those with a lower capacity for liver metabolism of imatinib, or low levels of albumin, a lower drug dose may be appropriate. Some investigators have suggested using positron emission tomography (PET) as a surrogate marker to determine whether dose escalation is needed. However, sufficient information is not yet available to justify this dosing approach.

4. Question: How should treatment responses be monitored?

New functional imaging techniques and biopsy specimen evaluations are likely to be useful for confirmatory evaluation of the response to treatment. The use of ^{18}F-fluoro-2-deoxyglucose for PET scanning (FDG-PET) provides greater information about the extent of disease and intratumoral metabolic activity than computed tomography (CT) [18]. Notably, FDG-PET showed evidence of a response to imatinib therapy before any measurable changes were seen on CT [18]. In some cases, FDG-PET detected treatment responses as early as 24 hours after starting imatinib. The biology underlying this noninvasive method requires further study. If PET is conducted, it is important that a high-quality system is used to ensure that small lesions or subtle differences are not missed. The spatial resolution achieved with an upgraded gamma camera system via single-photon emission computed tomography (SPECT) is much higher than the resolution achieved with dedicated PET. In terms of biopsy evaluations, the American College of Surgeons Oncology Group (ACOSOG) protocol will evaluate the benefit of adjuvant imatinib after complete resection in high-risk patients without metastases [8]. Significant amounts of tissue should be available for biopsy evaluations of the benefits of surgery and subsequent imatinib therapy.

In the evaluation of imatinib treatment in GISTs, intratumoral bleeds and edema around the lesion have been reported. Intratumoral bleeds are generally not seen during the first week of therapy but may occur several weeks later; their occurrence may reflect lysis of the tumor, with a subsequent good response achieved. Physicians should not hesitate to have a surgeon intervene and then continue imatinib therapy because of the possibility of ultimate clinical benefit. Edema around the tumor lesion should not be construed to reflect progressive disease if the PET scan has become negative, because some lesions increase in apparent size when they become more cystic.

5. Question: What is the role of surgery after the administration of imatinib?

Most patients with advanced GISTs have partial responses to imatinib therapy, but few achieve complete responses [11]. Accordingly, the issue of surgical resection once patients have reached their maximal response to drug therapy needs to be considered. In the design of the phase III trials, the possibility of surgical resection after a maximal response was not excluded. It is important to recognize, however, that the majority of patients in these trials are definitively unresectable, inasmuch as they have numerous sites of disease. Nevertheless, a subset of patients have two or three dominant masses, and could become surgical candidates if the tumors shrink substantially. For this subset of patients, investigators at the M.D. Anderson Cancer Center are evaluating the role of surgery. Other groups are likely to also consider a surgical approach in the future for patients whose tumors regress and then stabilize.

The role of surgery in advanced GISTs may differ depending on whether patients have undergone previous surgery or are presenting with metastatic disease. On the basis of data from Memorial Sloan-Kettering Cancer Center, a second surgical procedure is rarely curative [19,20]. However, in front-line therapy of metastatic disease, the benefit of surgery may differ. Accordingly, it will be interesting to analyze the subset data of the phase III studies to

identify which patient and tumor characteristics predict a better response to surgery after imatinib therapy.

6. Question: Are there molecular techniques to establish response to imatinib?

At some point, it will be important to ascertain which molecular and pathological lesions respond to imatinib, and then use molecular techniques to establish whether or not minimal residual disease remains after treatment. This information will define whether treatment has provided a pathologic and molecular complete remission. Practically all GISTs have constitutive activation of the KIT protein, and up to 90% of GISTs have mutated KIT [21]. Most commonly, mutations occur in exon 11, affecting the juxtamembrane domain of *KIT*, but mutations have also been found in exon 9 (located in the extracellular domain of the receptor) and in exons 13 and 17, which involve the tyrosine kinase domain [3,10,22]. Further validation of the incidence and types of mutation, and how the *KIT* mutational status will affect the clinical activity of imatinib, remain to be elucidated. Moreover, in situations where treatment does not prove to be initially effective or durable, it will be important to understand the mechanisms of resistance; in such cases, biopsy specimens will be required. Even in CML patients, where malignant cells and blast crisis could be studied in blood, an extraordinary amount of work was necessary to discover which mechanisms of resistance were involved. Accordingly, an organized strategy will be needed to analyze the biochemical and genetic characteristics of patients who do not respond or do not maintain a response to imatinib.

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