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Gastrointestinal stromal tumours: three perspectives on current diagnosis and therapy

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Gastrointestinal stromal tumours (GISTs) are rare neoplasms of the gastrointestinal tract that pose a potentially lethal clinical outcome. Classification of GISTs by pathologists has been controversial because the histologic appearance of GIST is often consistent with other tumours such as leiomyomas and leiomyosarcomas [1]. This lack of clarity in distinguishing GIST can potentially affect clinical decision-making, because non-GIST tumours included in the differential diagnosis are sensitive to systemic chemotherapeutic treatment, whereas GIST is resistant. Indeed, surgical resection was historically the only therapy with demonstrated, albeit short-term, efficacy in true GIST [2]. However, even complete surgical resection of primary GIST carried a substantial risk for recurrence, ie, surgery alone rarely resulted in a cure.

Recent insights into the molecular pathogenesis of GIST have further delineated these tumours as a distinct clinicopathologic entity. The hypothesis that GIST derives from the cell lineage normally giving rise to interstitial cells of Cajal (ICCs) was based, in part, on observations that both ICCs and GISTs express the receptor tyrosine kinase KIT [3]. Subsequent discoveries leading to the realisation that constitutively activating mutations of the *KIT* gene underlie most GISTs substantially advanced our understanding [4]. Identification of KIT as a key molecular mediator of GIST oncogenesis positioned it as both a specific diagnostic marker for GIST and a therapeutic target for pharmacologic intervention.

Imatinib is a small-molecule, relatively specific inhibitor of type III receptor tyrosine kinases including KIT, platelet-derived growth factor receptors (PDGFRs), and c-FMS, as well as BCR-ABL, ABL, and ARG tyrosine kinases [5–9]. The mechanism of action of imatinib in GIST involves inhibition of KIT or PDGFRα kinase activity and consequent suppression of signal transduction pathways linked to cell proliferation and resistance to apoptosis. As the first systemic therapy indicated for metastatic or unresectable GIST, imatinib has dramatically improved the outcome of patients with advanced GIST, particularly as compared with previous therapies [10–14]. As imatinib has become standard first-line therapy for advanced GIST, a wealth of clinical experience from trials and the real-world setting is available to refine recommendations for optimising treatment strategies. There are now guidelines for optimal dosing and duration of treatment with imatinib, as well as management of adverse events and measures to take when confronted with resistance [15,16].

The three papers presented in this supplement, authored by internationally recognised clinical investigators in sarcoma oncology, each focuses on a different aspect of the evolving clinical experience with GIST. The first article, by Dr Heikki Joensuu, entitled *Current perspectives on the epidemiology of gastrointestinal stromal tumours*, provides the foundation for the supplement, by outlining the scope of the medical need in GIST. Discussions of GIST incidence and prevalence, use of KIT immunoreactivity as a modern diagnostic criterion, and an overview of intrinsic prognostic factors in GIST are each presented. Molecular analyses of GIST, including the role of tumour genotype in determining responses to imatinib therapy and the molecular basis of imatinib resistance, are then discussed in the second article, by Dr Michael Heinrich, entitled *Molecular basis for treatment of gastrointestinal stromal tumours*. Finally, in an article entitled *Optimising therapy for GIST patients*, Dr Peter Reichardt provides an up-to-date overview of new evidence from trials investigating issues related to imatinib efficacy, dosing, and duration of therapy as well as strategies to manage resistance.

Additionally, the paper by Dr Reichardt provides overviews of the role of imaging in diagnosis and staging of GIST. Discussions revolve around the advantages and drawbacks of anatomic and functional imaging modalities, as well as the unique difficulties in assessing response and surveilling patients during imatinib therapy for GIST. Imatinib therapy for GIST has revealed inadequacies in the current solid tumour size-based response assessment

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criteria, such as Response Evaluation Criteria in Solid Tumors (RECIST) [17]. RECIST criteria can underestimate responses and/or overall progression, when based on standard computed tomography images of GIST.

The cornerstone of systemic GIST therapy is the drug imatinib. The first proof-of-concept experience with imatinib in a clinical setting was derived from treatment of a single advanced patient with GIST [18]. Since then several phase I, II, and III trials have demonstrated the efficacy of imatinib in patients with metastatic or unresectable GIST [10,11,14,19]. These trials consistently establish that high rates of partial response and disease stabilisation are obtained with imatinib therapy in metastatic or unresectable GIST. Rates of tumour control, which include rates of complete and partial response as well as stable disease, range from 74% to 90% across all trials. Durability of responses in advanced GIST has also been shown [20]. Stable disease can confer symptomatic benefit but, more importantly, evidence that patients with stable disease realise a clinical benefit is derived from the observation that there are no differences in survival rates between patients with GIST achieving partial responses on imatinib and those with stable disease.

An interesting discussion point is the fact that molecular characterisation of the genes encoding KIT or PDGFRα in GISTs correlates strongly with response, time-to-treatment failure, and survival in imatinib-treated patients [21–23]. The vast majority of GISTs harbour mutations in regions of the *KIT* gene that encode autoregulatory domains of the kinase molecule. These mutations occur predominantly in *KIT* exon 11 (66%) or exon 9 (10%), with a small percentage of GISTs harbouring mutations in *KIT* exon 13 or 17. Instead of mutated *KIT*, a few GISTs carry mutations in the gene encoding PDGFRα, which are most frequently observed in exon 18 [24,25]. Approximately 14% of GISTs have no detectable mutation in the genes encoding either of these receptor tyrosine kinases.

Several trials have revealed that patients with GISTs harbouring *KIT* exon 11 mutations had the highest response rate compared with other mutations [21–23]. Patients with advanced GIST with wild-type *KIT* or *PDGFRA* were the least responsive to imatinib therapy, yet some patients did respond. Thus, even patients with GISTs that do not show detectable mutations should be offered imatinib therapy. Additionally, improved imatinib response rates in patients with GISTs harbouring *KIT* exon 11 mutations translated into prolonged overall survival compared with patients with GISTs harbouring *KIT* exon 9 mutations or wild-type *KIT*.

Also, more than 95% of GISTs express detectable KIT, yet the level of KIT immunostaining does not correlate with imatinib response in patients. There are a number of possible underlying explanations for this apparent paradox. In a phase III trial of imatinib therapy, estimated 2-year progression-free survival rates were comparable between patients bearing GISTs with detectable and undetectable KIT [26]. Imatinib therapy should not be withheld from a patient with a tumour morphologically consistent with GIST but lacking KIT immunostaining.

Trials have been designed to investigate the most appropriate imatinib dose for treatment of advanced GIST. Significant differences in response rates were not observed between patients randomised to 400 mg or 600 mg once daily within one phase II trial [10]. Two randomised phase III trials were designed to directly compare efficacy and toxicity in patients with advanced GIST receiving imatinib, 400 mg po once or twice daily [19,27]. Although an increase in progression-free survival at 2 years with the higher dose of imatinib was observed in both studies, the difference was statistically significant in only one trial. For now, most experts recommend initiating imatinib therapy for patients with advanced GIST at a dose of 400 mg/day. Retrospective genotype analysis is underway from completed trials, to help determine whether specific subsets of patients should start with a higher dose.

Clinical experience with imatinib has raised questions about the duration of therapy required for optimal outcome. Clear evidence from trials described in these papers argues in favour of continued imatinib therapy in responding or stable patients with GIST. Discontinuation of imatinib therapy in such patients has produced rapid disease reactivation and progression [28,29]. Although disease control is often regained by reintroduction of imatinib in these patients with GIST, discontinuation of imatinib therapy poses an unnecessary risk for permanent loss of tumour control.

Imatinib resistance, detailed heavily in these reviews, is an increasingly important problem for treated patients with GIST. Resistance to imatinib in GIST can be defined as primary, meaning a response or period of stable disease is never observed, or secondary, when progression follows some degree of tumour control with imatinib. Resistance rates observed in the USA–Finland phase II trial were approximately 12% for primary resistance; 14% of patients demonstrated refractory disease after 6 months of imatinib therapy, and more than 50% of patients experienced some form of treatment failure after 2 years [10,20]. The molecular mechanisms underlying resistance are just beginning to be understood.

One simple measure to overcome imatinib resistance, based on the potential mechanism of target amplification, involves dose escalation up to 800 mg. Both phase III trials discussed above allowed patients on the 400 mg per day arm to cross over to the higher-dose arm after experiencing progression. A substantial number of these patients achieved disease stabilisation or, more rarely, partial responses, justifying the recommendation for dose escalation as a potential first course of action in cases of GIST progression on the standard dose of imatinib.

Taken together, the papers in this supplement provide a comprehensive source of GIST information, encompassing a broad spectrum of current diagnostic and therapeutic issues. As the era of targeted therapy in oncology continues

to unfold and new agents become available, this is an opportune time to review and consolidate the lessons learned from the imatinib experience in GIST.

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