Improving diagnosis and treatment of gastrointestinal stromal tumor (GIST) patients: Results from the Dutch GIST Registry

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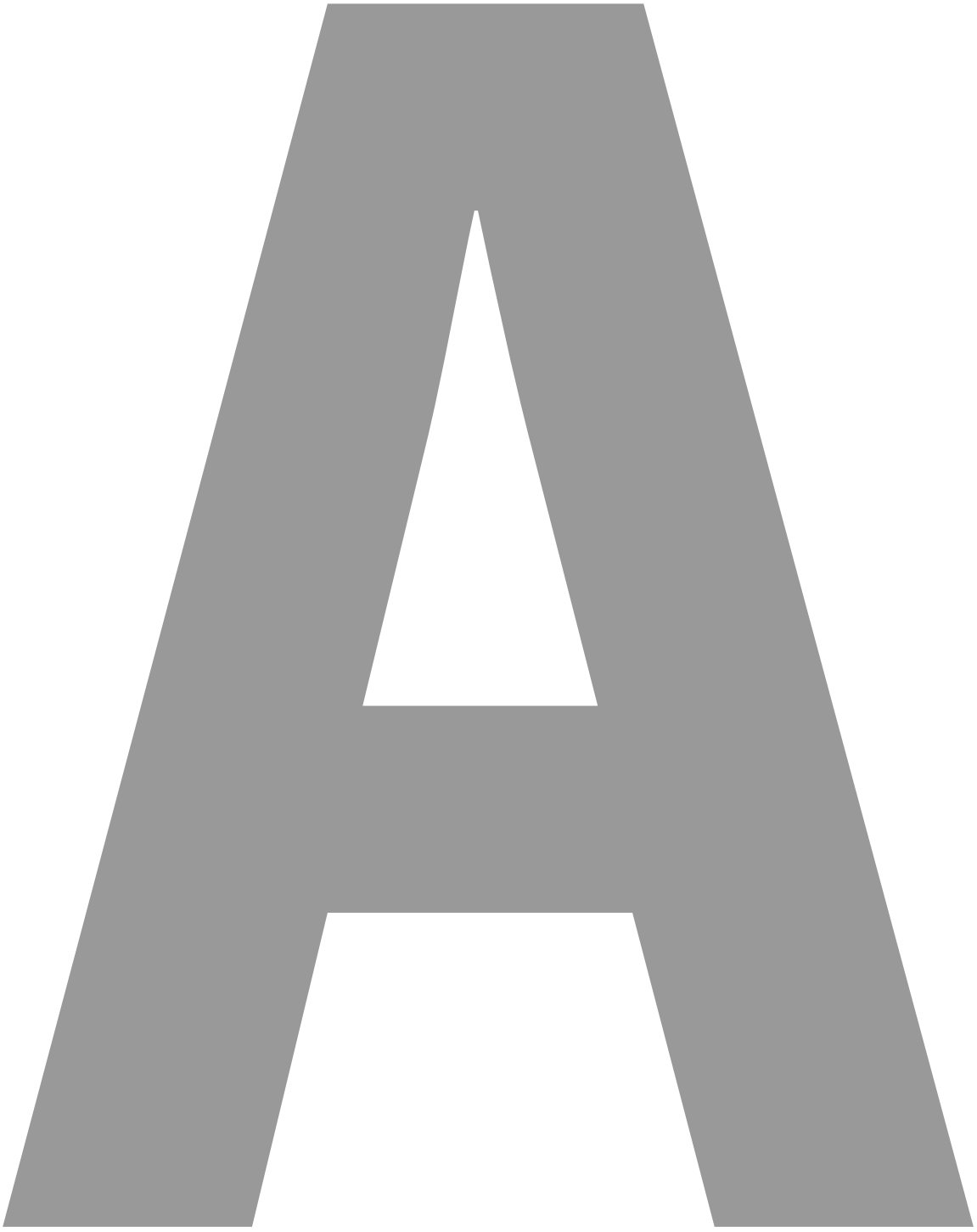

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Summary

Gastrointestinal stromal tumor (GIST) is a rare mesenchymal malignancy in the gastrointestinal tract. Since the introduction of imatinib in 2002, a tyrosine kinase inhibitor (TKI) that targets Bcr-Abl, KIT and PDGFR, treatment of patients with advanced GIST has been spectacularly improved. In this rapidly evolving field, more insight is needed the treatment and follow-up of GIST patients. The focus for this thesis is on treatment strategies and follow-up in GIST patients in daily clinical practice using a large comprehensive multicenter database.

In Chapter 2 different subtypes of GIST are discussed. One of the highest incidences of GIST is found in the age group of patients 75 years of age and older. In paragraph 2.1 we found that irrespective of performance status or comorbidity, elderly GIST patients (75 years and older) with localized disease received less treatment. Surgery was significantly less performed and in case of resection of a high-risk tumor, adjuvant treatment was given significantly less in elderly patients. Meanwhile, both primary resection and adjuvant imatinib treatment seem feasible and effective treatments in elderly GIST patients with localized disease. An objective evaluation of comorbidity using the CCI might improve the decisions-making process in elderly GIST patients.

In paragraph 2.2 we studied the most common *PDGFRA* mutation, a D842V substitution in exon 18, shows primary resistance to imatinib in in vitro and in vivo studies. Although D842V-mutated GISTs comprise a large majority of *PDGFRA* exon 18 GISTs, other mutations in exon 18 differ in their sensitivity to imatinib. It is therefore important to distinguish between resistant and sensitive mutations. Interestingly, we showed that a small fraction of D842V-mutated GISTs respond to treatment with imatinib. Therefore, in our view imatinib treatment should not be universally denied in D842V-mutated GISTs who are not surgically resectable.

The last paragraph on subgroups, paragraph 2.3, describes the effects of imatinib on the GISTs and the cutaneous hyperpigmentation associated with a germline *KIT* mutation (p.Trp557Arg) in two related GIST patients. Additionally, we give an overview of literature on the effect of imatinib in GIST patients harboring a germline *KIT* mutation. We show a remarkable and long term effect of imatinib in the GISTs and a striking effect on the pigmentation anomalies of the skin. Imatinib treatment should therefore be considered in these patients.

In Chapter 3 we studied hematological toxicities, since it remains unclear which patients are at risk for developing hematologic toxicity. A low ANC and low hemoglobin concentration at the initiation of imatinib are potential risk factors. In paragraph 3.1 we describe the occurrence and management of imatinib induced agranulocytosis. In our cases, neutropenia occurred within approximately one month after initiation of imatinib. In case of clear agranulocytosis, cessation of imatinib treatment remains crucial to avoid further hazardous exposure. All our patients experienced full recovery of the neutrophil

count only a few days after discontinuation of imatinib. Reintroduction of imatinib was in all our cases successful. We therefore recommend a re-challenge with imatinib is usually effective in locally advanced and metastatic GIST and a re-challenge with imatinib after a first episode of agranulocytosis and full recovery of the neutrophil count.

International guidelines recommend early response assessment by FDG-PET in patients treated with neo-adjuvant intent to prevent delay of surgery. However, to date no prior study has assessed the actual influence of FDG-PET on treatment strategies. In Paragraph 4.1 a nationwide series of imatinib treated GIST patients harboring non- *KIT* exon 11 mutations FDG-PET scans made for early response evaluation in the neo-adjuvant setting results in a change in management in half of the cases. We therefore advise to consider FDG- PET evaluation in this curative setting. Paragraph 4.2 on the other hand shows no benefit of early response evaluation using FDG-PET in patients treated in palliative setting. In case of a predefined indication over half of the late response FDG-PETs has led to change in management.

Several trials have found a correlation between higher imatinib plasma concentrations and better response to treatment in GIST and CML. In Chapter 5 we found that a large proportion of patients was underexposed to imatinib. This suggests that patients in routine care have a higher risk for underexposure, which may even result in less clinical benefit.

In conclusion, GIST is a rare disease and although treatment has spectacularly improved, for many subgroups more research is still needed. Considering the rarity of this tumor multicenter studies are necessary to acquire data on a sufficient number of patients. The Dutch GIST registry is a good example of a successful multicenter collaboration, resulting in increased research on GIST leading to an improvement in life expectancy and quality of life of current and future GIST patients.