

Tyrosine kinase inhibitors for cancer treatment

Citation for published version (APA):

Tullemans, B. M. E. (2021). *Tyrosine kinase inhibitors for cancer treatment: effects on platelets*. [Doctoral Thesis, Maastricht University]. ProefschriftMaken. <https://doi.org/10.26481/dis.20211006bt>

Document status and date:

Published: 01/01/2021

DOI:

[10.26481/dis.20211006bt](https://doi.org/10.26481/dis.20211006bt)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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The image features a dark teal background. In the top-left and bottom-left corners, there are clusters of semi-transparent, glowing spheres in various colors including blue, green, yellow, and cyan. The word "Impact" is written in a light green, italicized sans-serif font in the middle-right area of the page.

Impact

Cancer is a leading cause of death worldwide, with almost 10 million deaths in 2020¹. One of the hallmarks of cancer is to chronically sustain cell proliferation caused by mutations in or amplification of oncogene-encoded proteins or growth factor receptors². As these proteins include (tyrosine) kinases, cancer cells are described to have abnormal kinase activity which is known to drive processes such as cell proliferation, differentiation, migration, survival and angiogenesis^{3,4}. In the past two decades, increased understanding of this process has resulted in the development of many small molecule tyrosine kinase inhibitors (TKIs) as targeted therapy for cancer. In current settings of cancer treatment, TKIs significantly increase the progression-free survival of patients upon (lifelong) treatment. As tyrosine kinases are present in many cell-types, long-term treatment is often associated with (serious) adverse events including bleeding.

Platelets are important players in haemostasis and platelet production and function rely on several tyrosine kinases, suggesting that platelet count and function may be affected by TKIs. Hence, this may play a role in the increased risk of bleeding observed upon treatment with several TKIs. Yet, knowledge on whether and/or how platelets are affected by TKIs is limited. Therefore, we aimed to provide more insights in the effects of different TKIs on platelet function. To define what was known on the relation between TKIs and platelets at the start of this research, in **Chapter 2** an overview is given of the currently used TKIs in cancer treatment and the effects on platelet function. In order to extend the existing knowledge, we investigated platelet responses in the presence of different TKIs *in vitro* and in cancer patients (**Chapter 3-7**). Throughout this thesis, we showed that the majority of TKIs inhibit platelet responses mediated by the collagen receptor glycoprotein (GP)VI, e.g. activation, aggregation and/or thrombus formation. In some cases (additionally) CLEC-2- or GPIIb-induced thrombus formation was inhibited by TKI treatment. These results unravelled parts of the underlying mechanism of platelet inhibition by these TKIs. As these mechanisms still remain incomplete or unknown for some TKIs, this could provide new fields of interest for fellow researchers. Furthermore, with our studies involving (specific) cancer patients upon TKI treatment (**Chapter 3, 5 and 6**), we were able to gain knowledge on the interactions between platelet traits and TKI levels in the blood of these patients. We found that in renal cell carcinoma patients not only platelet function, but also platelet count, was affected by the TKIs sunitinib and pazopanib. For sunitinib, we discovered that the (active) compound levels in plasma or serum correlated with platelet count and function in these patients. This effect was measured already two weeks after the start of treatment, while response to therapy is normally not monitored until three months after start of treatment by a CT-scan. These plasma concentrations of sunitinib (or its metabolite) could be of importance for toxicity and the response to treatment, pointing towards platelets as a monitoring tool for compound effects, both on- and off-target. These results could be of interest for clinicians and cancer patients (hopefully) resulting in (early) therapeutic drug monitoring and increased quality of life during treatment. Therefore, more studies on the unintended side effects/off-target effects of drugs (not only on platelets, but

also other cells) could be of great importance to provide ways to monitor and improve treatment. These studies would enhance our understanding of the exact mechanism underlying the side effects, which could lead to the development of new drugs with reduced side effects.

Cancer patients often have a cardiovascular history^{5,6} and are prescribed with anti-platelet or anti-coagulant drugs to prevent recurrent cardiovascular events. As anti-platelet medications, such as clopidogrel and aspirin, are also associated with an increased bleeding risk⁷⁻⁹, in **Chapter 4** we examined whether there are synergistic effects on platelet function of dual treatment that could further increase the bleeding risk in TKI-treated cancer patients. We showed that aspirin aggravated the effects of sunitinib in platelet aggregation as well as delaying platelet-dependent coagulation in whole blood perfusion over a collagen surface. With these results we would like to raise awareness among clinicians of combining anti-platelet therapies and TKIs as this may result in an increased bleeding risk in patients.

As current anti-platelet therapies are associated with bleeding and thrombotic events may still occur, there is a need of better anti-thrombotic drugs. The platelet GPVI and CLEC-2 receptors are important players in arterial thrombosis and thrombo-inflammation with supporting roles in haemostasis¹⁰. A deficiency of GPVI or CLEC-2 does not significantly influence haemostasis^{11,12}, making these receptors interesting targets for anti-thrombotic drugs^{10,13}. As these receptors rely on tyrosine kinases for their underlying signalling pathways, we studied the anti-platelet properties of several clinically used TKIs with the aim to explore possible repurposing of these compounds as anti-platelet drugs. As several of the tested TKIs are described with only minor bleeding events, the GPVI inhibition observed with these TKIs might suggest that these could be promising candidates as anti-platelet drugs. However, more research with regard to dosage to estimate efficacy and toxicity in thrombotic patients is needed. With additional research, repurposing TKIs could be of great interest for clinicians, in particular cardiologists, as these TKIs are well-tolerated and already orally available in the clinic.

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