Role of Imatinib in treatment of GIST

Meta-analysis Submitted for

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Content

Abbreviations

GISTs	:	Gastro intestinal stomal tumors.
GI	:	GastroIntestinal.
KIT	:	proto-oncogene receptor tyrosine kinase.
PDGFRA	:	platelet-derived growth factor receptor alpha.
SCF	:	Stem Cell Factor.
TK1	:	Tyrosine Kinase 1 (ATP Binding pocket).
TK2	:	Tyrosine Kinase 2 (Kinase Activation Loop).
ICCS	:	Interstitioal Cells of Cajal.
EC	:	Extracellular.
TM	:	Transmembrane.
JM	:	Juxtamembrane.
GCH	:	comparative genomic hybridization.
SDHA	:	Succinate dehydrogenase complex, subunit A.
SDHB	:	Succinate dehydrogenase complex, subunit B.
SDHC	:	Succinate dehydrogenase complex, subunit C.
SDHD	:	Succinate dehydrogenase complex, subunit D.
HRAS	:	human homolog of the H-ras oncogene present in Harvey rat sarcoma virus.
NF1	:	neurofibromin 1.
DOG1	:	Discovered on GIST-1.
HE	:	Hematoxylin and eosin stain.
TKIs	:	Tyrosine Kinase Inhibitors.
EUS	:	Endoscopic Ultrasonography.
SMT	:	Submucosal Tumor.
EUS-FNA	:	Endoscopic Ultrasonography Fine-needle aspiration Biopsy.
CT	:	Computed Tomography.

Abbreviations

NIH	:	National Institute of Health.
AJCC	:	American Joint Committee on Cancer.
AFIP	:	Armed Forces Institute of Pathology.
Mit	:	Mitosis.
Hpf	:	High-powered feld.
ESMO	:	Eurpean Sarcoma Network Working Group.
NCCN	:	The National Comprehensive Cancer Network.
MDJC	:	Multidisciplinary Joint Clinic.
RR	:	Response Rate.
CR	:	Complete Response.
PR	:	Partial Response.
SD	:	Stable Disease.
DSR	:	Disease Stabilization Rate.
PD	:	Progressive Disease.
OS	:	Overall Survival.
STI	:	signal transduction inhibitor - protein-tyrosine kinase inhibitor.
c-Abl	:	Cytoplasmic-Abelson murine leukemia.
ATP	:	Adenosine Triphosphate.
CML	:	Chronic Myeloid Leukemia.
PFS	:	Progression Free Survival.
RFS	:	Recurrence Free Survival.
PK	:	Pharmacokinetics .
PD	:	Pharmacodynamics.
Cmax	:	Peak Plasma Concentration.
AGP	:	Acid Glycoprotein.
CYP	:	Cytochrome P Enzyme.
CGP	:	chorionic growth hormone-prolactin.
OCT		organic cation transporter.

Abbreviations

OATP	:	organic anion transporting polypeptide.
AUC	:	The area under the plasma concentration-time curve.
WT	:	Wild Type.
ADAGIO	:	Adherence Assessment with Glivec Indicators and Outcomes study.
TDM	:	Therapeutic Drug Monitoring.
BLT	:	Blood Level Testing.
LC-MS/MS	:	Liquid Chromatography-Tandem Mass Spectrometry.
PET	:	Positron Emission Tomography.
WHO	:	World Health Organization.
LFTs	:	Liver Function Tests.
RECIST	:	The Response Evaluation Criteria in Solid Tumors.
FDG	:	Fluorodeoxyglucose.
MDT	:	multidisciplinary team.
RFA	:	Radiofrequency ablation.
CrCL	:	Creatinine Clearance.
PRISMA	:	Preferred Reporting Items for Systematic Reviews and Meta-Analysis.
MOOSE	:	Meta-analysis of Observational Studies in Epidemiology.
ICJME	:	International Committee of Medical Journal Association.
RCTs	:	Randomized controlled trials.
OR	:	Odds Ratio.
CIs	:	Confidence Intervals.
SD	:	Standard Deviation.
MD	:	Mean Difference.
SMD	:	Standardized Mean Difference.
ACSOG	:	American College of Surgeons Oncology Group.
EORTC	:	European Organisation for Research and Treatment of Cancer.

List of Tables

List of Figures

List of Figures

Abstract

Abstract

Background: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor located in the gastrointestinal (GI) tract. Characteristically, most GISTs (> 95%) are positive for KIT (CD117) protein staining. Imatinib (also known as “Gleevec” or “Glivec”), a tyrosine kinase inhibitor, was called as “magical bullet,” when it revolutionized the treatment of chronic myeloid leukemia (CML) in 2001. **Aim of the Work:** To evaluate the efficacy and safety of two dose of imatinib treatment for patients with GISTs, a meta-analysis was performed. **Materials and Methods:** this systematic review and meta-analysis in accordance to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and (Meta-analyses Of Observational Studies in Epidemiology (MOOSE) statement. PRISMA and MOOSE are a reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of interventional and observational studies. **Results:** the overall effect estimates favoured Imatinib 400mg compared to no treatment in term of recurrent-free survival and overall survival **Conclusion:** adjuvant Imatinib is effective in patients with high risk GISTs, with tolerable safety profile.

Key words: Imatinib, treatment, GIST

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract, with an annual incidence of 10–15 cases per million. GISTs most commonly arise from the stomach (50–60 %) and small bowel (30–35 %) and less frequently arise from the colon and rectum (5 %) ***(Bischof et al., 2015)***.

The main treatment modality for primary GIST is complete surgical resection. Surgery alone for primary GIST is associated with a 5-year recurrence-free survival of 70 %.While many patients with GIST have an excellent prognosis, patients with large tumors, a high mitotic rate, non-gastric location and tumor rupture are at higher risk for recurrence ***(Joensuu et al., 2012)*** .

Approximately, 75 % of patients with GIST have mutations in the receptor tyrosine kinase KIT (CD117) that lead to KIT overexpression. The CD-117 by almost (80-95%) molecule is part of the KIT receptor tyrosine kinase that is a product of the KIT proto-oncogene. This gene encodes a transmembrane receptor for a growth factor named stem cell factor (SCF). Binding of SCF to KIT induces KIT dimerization and activation. Constitutive activation of KIT signaling leads to uncontrolled cell proliferation and inhibition of apoptosis. The KIT product is expressed on the interstitial cells of Cajal, mast cells, and melanocytes, but a mesenchymal spindle cell tumor in the GI tract that stains diffusely positive for CD117 is characteristic of a GIST ***(Dossett & Merchant, 2015)***.

KIT mutations generally occur in one of four of the 21 exons of the gene. The most common mutation is of exon 11 which encodes for the intracellular component of the transmembrane portion, but mutations of exon 9 (the extracellular component of the transmembrane portion) are also common (7 %). Mutations of exon 13 and exon 17 are rare. Mutations make KIT function independent of activation, leading to a high rate of mitosis and genomic instability. A small percentage of GISTs (5–7 %) have a mutation in the platelet-derived growth factor receptor-alpha (PDGFRA) instead of the more common KIT mutation. PDGFRA is a receptor tyrosine kinase which shares extensive similarities with KIT, but the mutations are distinct in that they do not respond to the same growth factors. Almost all GISTs will harbor either the KIT or PDGFRA mutation, but not both since each is an alternative path to uncontrolled proliferation As many as 60 % of PDGFRA mutations occur in exon 18 . Emerging data suggest that mutation type has important implications for prognosis, recurrence, response to therapy, and the development of tyrosine kinase inhibitor resistance ***(Joensuu & DeMatteo, 2012)***.

The treatment strategy of GISTs varies depending on size and tumor location. Complete surgical extirpation remains the cornerstone of GIST management and the only curative treatment. When GISTs are densily adherent to adjacent organs, en bloc resection should be performed. These tumors should also be carefully handled to avoid tumor rupture, which lead to avery high risk intra-abdominal dissemination and recurrence. Because GISTs rarely metastasize to lymph nodes, formal lymphadenectomy is not necessary ***(Shen et al., 2015)***.

The outcome of surgery alone have been inadequate, with up to 50% of patients developing tumor local or distant recurrence, with a median time to recurrence of 2 years, and eventually dying from the

disease. GISTs are notoriously unresponsive to chemotherapy and radiation therapy. With the success of imatinib in the treatment of metastatic GIST, this has prompted investigation into the potential benefit of adjuvant imatinib. Imatinib mesylate is a small molecule that inhibits activation of the KIT and PDGFa proteins by binding to the adenosine triphosphate binding pocket required for receptor phosphorylation and activation. The role of adjuvant imatinib therapy is being actively investigated ***(Dematteo et al., 2013)*** .

Tyrosine kinases are key targets in oncology, as they play an important role in the modulation of growth factor signalling. Imatinib is an oral inhibitor of the KIT and platelet-derived growth factor receptor-tyrosine kinases, which are frequently mutated in gastrointestinal stromal tumors (GISTs). Imatinib is effective in treating patients with chronic myeloid leukemia (CML), GIST and dermatofibrosarcoma. Imatinib is indicated for first-line treatment of patients with unresectable and/or metastatic GIST, and also is approved as adjuvant therapy for patients following resection of primary KIT-positive GIST .Imatinib is generally well tolerated. Most adverse events are manageable and are often transient or self-limiting .The adverse events commonly experienced include nausea and vomiting, diarrhea, musculoskeletal complaints, skin rash, fatigue, hemorrhage, edema, and hematological toxicity . However, with careful use of supportive care, most can be managed without dose reduction or interruption of treatment. In the event of severe toxicity, individualized tailoring of the dose may be required ***(Nishida et al., 2016).***

In patients with advanced disease resistant to Imatinib , sunitinib is asafe and effective second line agent ***(Raut CP et al.,2010)*** .

While several third line agents such as sorafenib, nilotinib, dosatinib and most recently vatalanib have been used in small limited numbers of patients with disease refractory to imatinib and sunitinib **(Joensuu et al., 2011)**.

Aim of the work

To evaluate the efficacy and safety of two dose of imatinib treatment for patients with GISTs, a meta-analysis was performed.