Review

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Advancement in medical treatment for gastrointestinal stromal tumors (GISTs): a ray of hope

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Abstract

Gastrointestinal stromal tumors (GISTs) present unique diagnostic and therapeutic challenges. This review highlights advancements facilitated by molecularly targeted therapies like imatinib for advanced, metastatic, and high-risk GISTs, underscoring their neoadjuvant/adjuvant utility and the importance of multidisciplinary care. Emerging avenues, including immunotherapy, PI3K/mTOR/HSP90 inhibitors, are examined, reflecting the evolving treatment landscape. Furthermore, it explores distinct clinical considerations for GIST subtypes like spindle cell, epithelioid, mixed, and SDH-deficient tumors. Crucially, identifying predictive biomarkers (molecular alterations, non-coding RNAs, SLITRK3 expression, aberrant DNA methylation, radiomics) is emphasized for optimizing individualized regimens and improving outcomes. Overall, the review highlights the remarkable advances in GIST treatment while emphasizing the need for ongoing research into novel, molecularly tailored therapeutic strategies.

Keywords: gastrointestinal stromal tumors, immunotherapy, molecular alterations, non-coding RNAs, predictive biomarkers

Introduction

Gastrointestinal stromal tumors (GISTs) pose several unique challenges in the field of gastroenterology[1]. GISTs are estimated to make up approximately 15 % of all soft tissue sarcomas[2]. The vast majority of GISTs (around 85%) occur sporadically, meaning they arise spontaneously without any clear hereditary or genetic predisposition[3]. GISTs are associated with Neurofibromatosis Type 1 (NF1), Carney Triad, Carney-Stratakis Syndrome (Carney Dyad), Familial GIST Syndrome. GISTs pose significant challenges for curative surgery due to their anatomic location, which can arise anywhere along the gastrointestinal tract, including areas difficult to access surgically like the esophagus or rectum, making complete resection complicated. Additionally, GISTs tend to be fragile tumors with a risk of rupture during surgical manipulation, leading to potential tumor seeding and spreading. A significant proportion of GISTs present with metastatic disease at diagnosis, often involving the liver or peritoneal cavity, where complete surgical removal of all tumor deposits may not be feasible. Even after an apparently complete resection, GISTs have a notable risk of recurrence, especially in cases with high-risk features like large tumor size or a high mitotic rate. Furthermore, in some instances, GISTs can occur as multifocal tumors in different locations, making it challenging to achieve complete surgical removal.

Methods

In this review article, we conducted a comprehensive search of the scientific literature to synthesize recent advances in gastrointestinal (GI) cancer. The search was performed across four major scientific databases – PubMed, Scopus, Web of Science, and Google Scholar – covering articles published in English. We employed a combination of key terms related to various aspects of GI cancer, including its epidemiology, pathophysiology, diagnosis, treatment, and molecular biomarkers. Specific search terms included "gastrointestinal cancer," "colorectal cancer," "gastric cancer," "esophageal cancer," "pancreatic cancer," "liver cancer," "biomarkers," "chemotherapy," "immunotherapy," and "molecular pathways," among others. Studies were included if they focused on human subjects, described original research or clinical trials related to any form of gastrointestinal cancer, and were published in peer-reviewed journals. Only studies that provided sufficient data on cancer epidemiology, molecular mechanisms, treatment modalities, or clinical outcomes were considered. We excluded case reports, editorials, conference abstracts, and studies not published in English, as well as those that did not

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present original research or did not focus specifically on gastrointestinal cancer.

Data extraction involved gathering key information from the selected studies, including study design, patient demographics, cancer type(s) investigated, key findings related to the molecular pathology of the cancer, treatment strategies, survival outcomes, and potential biomarkers or therapeutic targets identified. These findings were synthesized narratively, with an emphasis on emerging trends in the molecular understanding of GI cancers and advancements in diagnostic and therapeutic approaches.

GISTs

The management of GISTs has evolved significantly in the last two decades due to a better understanding of their biological behavior and the development of molecularly targeted therapies[4]. GISTs pose a challenge in treatment due to the limited success of curative surgery in some cases. However, the advent of molecularly targeted therapies, particularly tyrosine kinase inhibitors (TKIs) like imatinib mesylate, has significantly improved the management of advanced and metastatic GISTs[5-7]. Imatinib therapy has revolutionized the treatment landscape for GISTs, offering options for advanced, metastatic, and high-risk GISTs, as well as serving as a neoadjuvant agent to reduce tumor size before surgical resection[8,9]. The efficacy of imatinib in adjuvant therapy has been demonstrated to enhance recurrence-free survival in GIST patients post-surgery[9]. Additionally, the multidisciplinary approach involving surgical and medical oncologists, pathologists, gastroenterologists, and radiologists is essential for optimal GIST patient care[10]. In addition to TKIs, other targeted therapies have emerged for GISTs. For instance, nivolumab has shown durable tumor regression in highly refractory metastatic GIST cases[11]. Furthermore, the combination of the PI3K inhibitor GDC-0941 with imatinib has demonstrated potent antitumor efficacy in GIST xenografts, inducing substantial tumor regression and apoptosis[12]. These novel therapeutic approaches highlight the evolving landscape of targeted therapies for GISTs. Furthermore, the emergence of regorafenib as a third-line therapy for advanced GIST after progression on imatinib and sunitinib has provided additional options for patients with metastatic disease[13]. Regorafenib's approval was based on a demonstrated survival benefit in patients with metastatic GIST who experienced disease progression after treatment with previous targeted therapies[14]. For instance, the investigation of mTOR inhibitors, such as everolimus, has demonstrated potential in preclinical studies, suggesting a role for targeting the mTOR pathway in GIST management[15]. Moreover, the exploration of HSP90 inhibitors, which target heat shock protein 90, exhibited antitumor activity in GIST models, offering a new avenue for therapeutic intervention[16]. Additionally, the identification of SDH-mutated GISTs has highlighted a subset of tumors that do not respond well to commonly used targeted therapies, such as imatinib, underscoring the importance of understanding tumor biology for personalized treatment approaches[17]. This emphasizes the need for ongoing research to explore alternative treatment strategies for GISTs with specific molecular profiles. In addition, Fig. 1 summarizes various common symptoms and therapeutic and surgical treatment strategies for GISTs. Moreover, the role of circulating tumor DNA in genetic analysis has provided insights into the genetic landscape of advanced GISTs, offering potential for more targeted and personalized treatment approaches based on individual tumor characteristics[18]. This highlights the importance of integrating molecular profiling into the management of GISTs to optimize treatment outcomes.

Spindle cell GISTs

Spindle cell GISTs pose a challenge in treatment, particularly when curative surgery is not as successful. While surgery remains the primary curative option for GISTs, including spindle cell types, in cases where surgical resection is not feasible or less

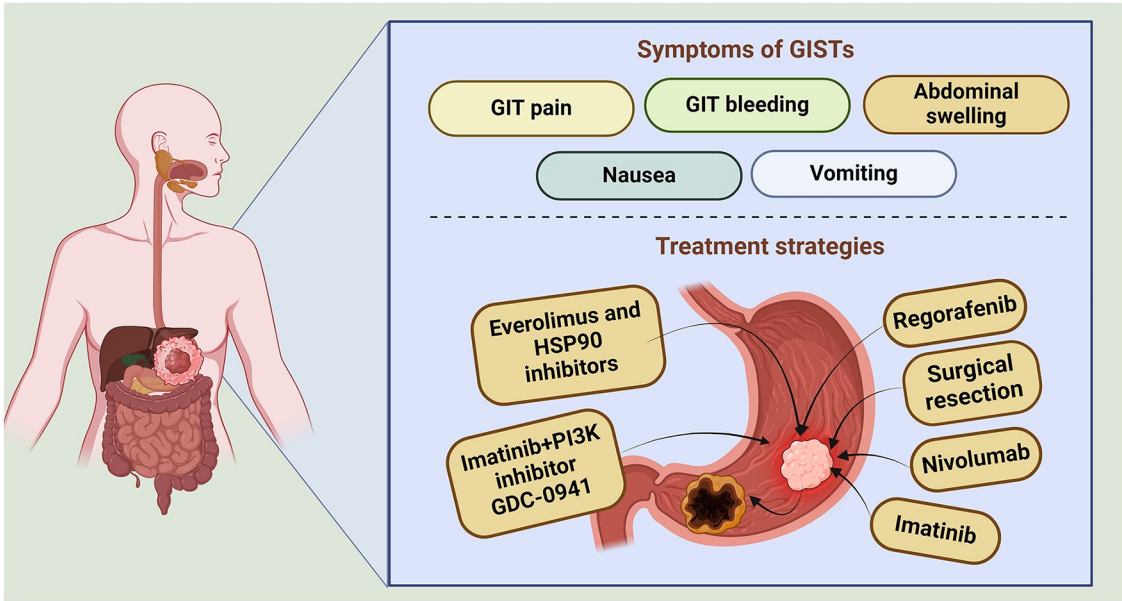

Figure 1. Summarization of various common symptoms and advancement in treatment strategies for GISTs (*Created with BioRender*).

effective, medical therapy plays a crucial role in managing these tumors[19]. The standard of care for GISTs, including spindle cell variants, involves a multidisciplinary approach, with surgery being the cornerstone of treatment for resectable GISTs[19]. Regarding spindle cell GISTs, the potential differential diagnoses may include leiomyoma, leiomyosarcoma, intra-abdominal desmoid fibromatosis, schwannoma, inflammatory myofibroblastic tumor, and solitary fibrous tumor[20]. However, the diagnosis of spindle cell GISTs is facilitated by the strong and diffuse positivity for CD117 in almost all cases, regardless of different genetic subtypes[21]. This immunohistochemical feature aids in distinguishing spindle cell GISTs from other spindle cell neoplasms. Additionally, the cytological features of spindle cell GISTs often overlap with other spindle cell neoplasms, such as smooth muscle and neural tumors, underscoring the importance of accurate diagnosis through fine-needle aspiration cytology[22]. Furthermore, the development of predictive biomarkers for treatment response in spindle cell GISTs could help tailor individualized treatment regimens based on tumor characteristics, optimizing therapeutic strategies and minimizing disease progression[23]. By advancing our understanding of the molecular landscape of spindle cell GISTs and exploring innovative treatment approaches, we aim to improve outcomes and quality of life for patients facing these challenging tumors. The formation of irregular GIST tumor and detection via endoscopy and endoscopic ultrasonography has been depicted in Fig. 2.

Epithelioid GISTs

In the management of epithelioid GISTs, targeted therapies are crucial in cases where curative surgery is not an option. Once the diagnosis of epithelioid GIST is confirmed via immunohistochemistry, genetic factors such as PDGFRA mutations or SDH deficiency are vital for guiding treatment decisions[24]. Research focusing on the molecular characteristics of epithelioid GISTs may offer insights into potential therapeutic targets and pathways for more effective treatment strategies[25]. For instance, Imatinib therapy; 400 mg daily, is often continued for an extended period, with treatment durations varying based on individual patient responses and disease progression[26,27]. Sunitinib is another TKI used in the treatment of GISTs, typically administered at a dose of 50 mg once daily on a 4-weeks-on and 2-weeks-off schedule[28]. Additionally, studies investigating the effectiveness of adjuvant therapies, such as targeted agents or immunotherapy, in epithelioid GISTs could present new opportunities for enhancing patient outcomes[29]. One of the promising drugs in immunotherapy for GISTs is ipilimumab, a cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor. The standard dose of ipilimumab used in combination therapy for Epithelioid GISTs is typically administered intravenously at a dose of 3 mg/kg every 3 weeks for a total of four doses[30]. Clinical trials exploring novel treatment modalities and combination therapies may provide valuable data on improving treatment responses and extending survival in patients with epithelioid GISTs[31]. Moreover, the identification of predictive biomarkers (Molecular alterations, such as mutations in KIT proto-oncogene receptor tyrosine kinase and PDGFRA genes, non-coding RNAs, SLITRK3 expression, Aberrant deoxyribonucleic acid (DNA) methylation patterns, Radiomics-based approaches) for treatment response in epithelioid GISTs could assist in tailoring individualized treatment regimens based on tumor characteristics, optimizing therapeutic strategies, and minimizing disease progression[32-38]. By advancing our comprehension

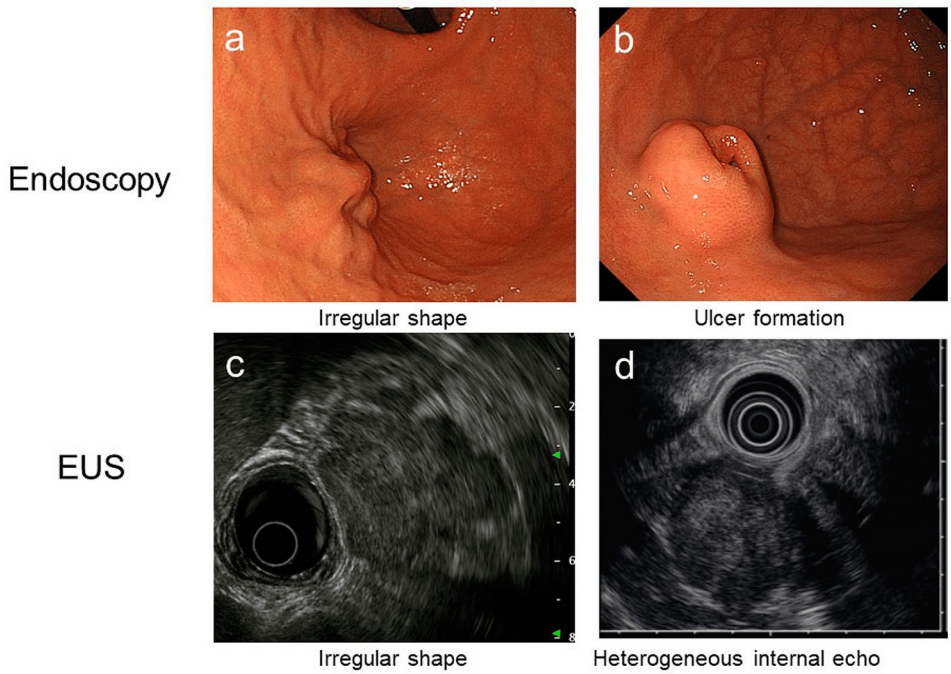

Figure 2. Depicted GISTs diagnostic images via endoscopy and endoscopic ultrasonography. (a) Demonstrated irregular shape of GIST detected via endoscopy. (b) Identified the ulcer formation via endoscopy. (c) Understanding of irregular shape of GIST via endoscopic ultrasonography. (d) Identification of heterogeneous internal echo via endoscopic ultrasonography in GIST tumor[38].

of the molecular landscape of epithelioid GISTs and exploring innovative treatment approaches, we strive to enhance outcomes and quality of life for patients grappling with these challenging tumors.

Mixed GISTs

In the context of mixed GISTs, the leading curative option is surgical resection, especially in the setting of primary resistance to imatinib therapy[39]. However, it has been demonstrated that debulking surgery combined with adjuvant drug therapy prolongs the overall survival of patients with metastatic primary GIST when compared with imatinib alone[40]. Additionally, knowledge of O-6-methylguanine-DNA methyltransferase promoter methylation status may offer a novel potential therapeutic option for Wild type GISTs with a mixed phenotype[31].

SDH-deficient GISTs

The treatment of SDH-deficient GISTs presents unique challenges due to the distinctive features of these tumors, including the absence of KIT proto-oncogene receptor tyrosine kinase/PDGFRA mutations, virtually exclusive gastric location, lobulated growth, multi-focality, and primary resistance to imatinib therapy[41]. SDH-deficient GISTs do not respond well to common targeted therapy, with no objective tumor response to imatinib[17]. However, the identification of a better molecular landscape in SDH-deficient GISTs may provide a wider window of potential therapeutic opportunities for this treatment-orphan GIST subtype[42]. At the molecular level, GISTs can be categorized into two groups based on the causative oncogenic mutations[43]. Additionally, altered chromosomal topology has been found to drive oncogenic programs in SDH-deficient GISTs, with implications for mechanistic targeting of aberrant pathways in cancers[44]. Immunohistochemical loss of succinate dehydrogenase subunit A (SDHA) in GISTs signals SDHA germline mutation, and the involvement of FGF/FGFR signaling in GIST pathogenesis has been established in different molecular subgroups[25,45]. Furthermore, SDH deficiency is associated with pervasive DNA methylation, which appears to be not randomly distributed, as evidenced by the significant number of recurrent hypo- and hypermethylated genomic targets found in these tumors[46]. The overexpression of insulin-like growth factor 1 receptor and frequent mutational inactivation of SDHA in wild-type SDHB-negative gastrointestinal stromal tumors have also been reported[47]. The treatment of SDH-deficient GISTs remains a challenge due to their unique molecular and clinical characteristics. The identification of specific molecular alterations and targeted therapies, along with a better understanding of the molecular landscape, holds promise for the development of more effective treatment strategies for this subtype of GISTs. Several clinical trials related to the management of GISTs are summarized in Table 1.

Future medical therapy in GISTs and Concluding remarks

Recent advances in the management of GISTs have explored treatment options such as radiotherapy, chemotherapy, hepatic

Table 1

Summarizes various clinical trials associated with GIST treatment or management in recent years

NCT number	Study title	Interventions	Age	Phases	Study type	Study starts and completion	References
NCT00385203	The biological activity of cediranib (AZD2171) in gastro-intestinal stromal tumors (GIST)	AZD2171	Adult, older adults	Phase 2	Interventional	2006-09, 2009-12	[48]
NCT02034110	Efficacy and safety of the combination therapy of dabrafenib and trametinib in subjects with BRAF V600E-mutated rare cancers	Dabrafenib, Trametinib	Adult, older adults	Phase 2	Interventional	2014-03-12, 2021-12-10	[49]
NCT00028002	Neoadjuvant and adjuvant imatinib mesylate in treating patients with primary or recurrent malignant gastrointestinal stromal tumor	Conventional Surgery, Imatinib Mesylate	Adult, older adults	Phase 2	Interventional	2002-03-31, 2009-01-28	[50]
NCT00457743	A Phase I/II study of sunitinib malate (SU011248) in patients with gastrointestinal stromal tumor (GIST)	Sunitinib malate (SU011248)	Adult, older adults	Phase 1, Phase 2	Interventional	2005-01, 2008-08	[51]
NCT01404650	Study of Hsp90 inhibitor AUY922 for the treatment of patients with refractory gastrointestinal stromal tumor	AUY922	Adult, older adults	Phase 2	Interventional	2011-12, 2015-02	[52]
NCT00278876	Adjuvant imatinib in high-risk gastrointestinal stromal tumor (GIST) with C-kit mutation	Imatinib mesylate (Glivec)	Adult, older adults	Phase 2	Interventional	2005-04, 2011-03	[53]
NCT01478373	Efficacy and safety of dovitinib in patients with gastrointestinal stromal tumors refractory and/or intolerant to imatinib	Dovitinib (TKI258)	Adult, older adults	Phase 2	Interventional	2012-01, 2014-07	[54]
NCT00623831	A Phase 1 study of mixed bacteria vaccine (MBV) in patients with tumors expressing NY-ESO-1 antigen	BIOLOGICAL: Mixed bacterial vaccine	Adult, older adults	Phase 1	Interventional	2007-05, 2013-05	[55]

(*Continued*)

Table 1

(Continued).

NCT number	Study title	Interventions	Age	Phases	Study type	Study starts and completion	References
NCT01874665	A Phase 2 trial of ponatinib in participants with metastatic and/or unresectable gastrointestinal stromal tumor	Ponatinib	Adult, older adults	Phase 2	Interventional	2013-06-05, 2016-07-31	[56]
NCT00464620	Trial of dasatinib in advanced sarcomas	Dasatinib	Child, adult, older adults	Phase 2	Interventional	2007-05, 2017-05	[57]
NCT01068769	Regorafenib in patients with metastatic and/or unresectable gastrointestinal stromal tumor	Regorafenib	Adult, older adults	Phase 2	Interventional	2010-02, 2020-08	[58]
NCT01560260	Linsitinib in treating patients with gastrointestinal stromal tumors	Laboratory Biomarker Analysis, Linsitinib, Pharmacological Study	Adult, older adults	Phase 2	Interventional	2012-03, 2015-10	[59]
NCT03465722	(VOYAGER) study of avapritinib vs regorafenib in patients with locally advanced unresectable or metastatic GIST	Avapritinib, Regorafenib	Adult, older adults	Phase 3	Interventional	2018-03-26, 2021-09-15	[60]
NCT00112463	Depsipeptide (romidepsin) in treating patients with metastatic or unresectable soft tissue sarcoma	Romidepsin	Adult, older adults	Phase 2	Interventional	2005-01-07, 2008-10-23	[61]
NCT01831726	Dovitinib for patients with tumor pathway activations inhibited by dovitinib	Dovitinib (TKI258)	Adult, older adults	Phase 2	Interventional	2013-08, 2015-12	[62]
NCT00867113	Five year adjuvant imatinib mesylate (GleevecÂ®) in gastrointestinal stromal tumor (GIST)	Imatinib mesylate	Adult, older adults	Phase 2	Interventional	2009-07-22, 2016-12-20	[63]
NCT00075218	A study to assess the safety and efficacy of SU11248 in patients with gastrointestinal stromal tumor (GIST)	Placebo, SU011248	Adult, older adults	Phase 3	Interventional	2003-12, 2008-05	[64]
NCT01039519	A study evaluating STA-9090 in patients with metastatic and/or unresectable gastrointestinal stromal tumor (GIST)	Ganetespib	Adult, older adults	Phase 2	Interventional	2010-01, 2011-12	[65]
NCT00793871	Safety and efficacy study of sunitinib malate in Chinese patients with imatinib resistant or intolerant malignant gastrointestinal stromal tumor	Sunitinib Malate (SU011248)	Adult, older adults	Phase 4	Interventional	2008-11, 2014-10	[66]
NCT03291288	Effect of pexidartinib on the way the body processes CYP3A4 and CYP2C9 substrates (pharmacokinetics)	Tolbutamide, Midazolam, Pexidartinib	Adult, older adults	Phase 1	Interventional	2018-02-26, 2021-04-16	[67]
NCT01271712	Study of regorafenib as a third-line or beyond treatment for gastrointestinal stromal tumors (GIST)	Regorafenib (Stivarga, BAY73-4506), Placebo, best supportive care	Adult, older adults	Phase 3	Interventional	2011-01-04, 2019-04-15	[68]
NCT00400569	Phase II study of sunitinib malate for metastatic and/or surgically unresectable soft tissue sarcoma	Sunitinib Malate (SU011248)	Adult, older adults	Phase 2	Interventional	2006-11, 2011-12	[69]
NCT02164240	Phase Ib study of sunitinib alternating with regorafenib in patients with metastatic and/or unresectable GIST	Sunitinib, Regorafenib	Adult, older adults	Phase 1	Interventional	2014-07, 2021-05	[70]
NCT00237185	A study of the efficacy and safety of imatinib mesylate in patients with unresectable or metastatic gastrointestinal stromal tumors expressing C-kit gene	Imatinib mesylate	Adult, older adults	Phase 2	Interventional	2000-06, 2013-06	[71]
NCT00471328	Efficacy and safety of nilotinib (AMN107) compared with current treatment options in patients with GIST who have failed both imatinib and sunitinib	Nilotinib, Best Supportive Care (BSC) ± imatinib or sunitinib	Adult, older adults	Phase 3	Interventional	2007-03, 2011-06	[72]
NCT01396148	A study of sunitinib in young patients with advanced gastrointestinal stromal tumor	Sunitinib malate dose escalation, Sunitinib malate	Child, adult	Phase 2	Interventional	2012-06, 2017-08	[73]

(*Continued*)

Table 1

(Continued).

NCT number	Study title	Interventions	Age	Phases	Study type	Study starts and completion	References
NCT02015065	Phase II trial of vandetanib in children and adults with wild-type gastrointestinal stromal tumors	Vandetanib	Child, adult, older adults	Phase 2	Interventional	2013-12-14, 2019-12-10	[74]
NCT00780494	Phase II of capecitabine, carboplatin & bevacizumab for gastroesophageal junction & gastric carcinoma	Bevacizumab, Carboplatin, Capecitabine	Adult, older adults	Phase 2	Interventional	2009-02, 2017-12-31	[75]
NCT01275222	Everolimus in combination with imatinib in patients with glivec refractory/resistant gastrointestinal stromal tumors	RAD001, Imatinib 600 mg/day, Imatinib 800 mg/day	Adult, older adults	Phase 1, Phase 2	Interventional	2002-11-13, 2008-09-03	[76]
NCT02257541	BGJ398 in combination with imatinib mesylate in patients with untreated advanced gastrointestinal stromal tumor (GIST)	BGJ398, Imatinib Mesylate	Adult, older adults	Phase 1, Phase 2	Interventional	2014-10-02, 2019-03-25	[77]
NCT00137449	Study of SU011248 administered on a continuous daily dosing schedule in patients with gastrointestinal stromal tumor	SU011248	Adult, older adults	Phase 2	Interventional	2005-09, 2008-04	[78]
NCT01151852	Re-challenge of imatinib in GIST having no effective treatment: RIGHT	Imatinib, Placebo	Adult, older adults	Phase 3	Interventional	2010-06, 2013-03	[79]
NCT02500797	Nivolumab with or without ipilimumab in treating patients with metastatic sarcoma that cannot be removed by surgery	Ipilimumab, Laboratory Biomarker Analysis, Nivolumab, Quality-of-Life Assessment	Adult, older adults	Phase 2	Interventional	2015-08-13, 2023-04-01	[80]
NCT01907607	Efficacy and safety of PD-0332991 in advanced gastrointestinal stromal tumors refractory to imatinib and sunitinib	PD 0332991	Adult, older adults	Phase 2	Interventional	2014-02, 2019-02	[81]
NCT00785785	A study of nilotinib versus imatinib in GIST patients	Nilotinib (AMN107), imatinib (STI571)	Adult, older adults	Phase 3	Interventional	2009-03, 2014-10	[82]
NCT01289028	Efficacy of nilotinib in adult patients with gastrointestinal stromal tumors resistant to imatinib and sunitinib	Nilotinib	Adult, older adults	Phase 3	Interventional	2008-11, 2014-07	[83]
NCT01154452	Vismodegib and gamma-secretase/notch signaling pathway inhibitor RO4929097 in treating patients with advanced or metastatic sarcoma	Gamma-Secretase Inhibitor RO4929097, Laboratory Biomarker Analysis, Vismodegib	Adult, older adults	Phase 1, Phase 2	Interventional	2010-06, 2015-02	[84]
NCT02508532	(NAVIGATOR) Study of BLU-285 in patients with gastrointestinal stromal tumors (GIST) and other relapsed and refractory solid tumors	Avapritinib	Adult, older adults	Phase 1	Interventional	2015-08, 2021-06-03	[85]
NCT01440959	Dovitinib for imatinib/sunitinib-failed gastrointestinal stromal tumors (GIST): TKI258	Dovitinib	Adult, older adults	Phase 2	Interventional	2011-09, 2013-03	[86]
NCT03353753	Phase 3 study of DCC-2618 vs placebo in advanced GIST patients who have been treated with prior anticancer therapies	DCC-2618, Placebo Oral Tablet	Adult, older adults	Phase 3	Interventional	2018-02-27, 2022-05-11	[87]

artery embolization, chemoembolization, and radiofrequency ablation for metastatic GISTs[88]. Additionally, molecularly targeted therapy, particularly with imatinib, has revolutionized the treatment of advanced GISTs and facilitated scientific research in this area[5]. However, the identification of a better molecular landscape in SDH-deficient GISTs may provide a wider window of potential therapeutic opportunities for this treatment-orphan GIST subtype[7]. The development of novel treatment strategies beyond the direct inhibition of KIT may become a crucial factor in GIST treatment in the near future[89]. Several investigational multi-kinase inhibitors (MKIs) such as nilotinib, dasatinib, or masitinib have been tested as first-line therapies in phase II/III studies, indicating the exploration of alternative treatment options[90]. Furthermore, the identification of kinase targets and the exploration of the majority of the kinome in GIST specimens from different molecular subtypes may lead to the development of novel therapeutic targets[91]. In addition, Table 2 further summarized the various clinical investigations of first-line therapeutics for the treatment of GISTs along with targeted therapy outcome. The future of GIST management also involves the critical selection of cases based on further research, as the role of surgery in advanced GIST remains a controversial

Table 2

Summarized the efficacy and adverse effects of various first-line therapeutic interventions along with mechanism of action in clinical settings for GIST treatment

S. No.	Therapeutic intervention, dose, route of administration	Study description/ objective	Mechanism of action	Method	Trial status	Results/outcome in targeted therapy	Year of publication	Trial registration No.	References
1.	Imatinib, 400 mg daily, Oral	To understand the long-term therapeutic intervention of oral imatinib for GIST treatment in BFR14 trial.	TKIs	An open-label, randomized trial in 17 cancer patients with advanced GIST, aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0-3, previous treatment with imatinib, and malignancy was not eligible.	Phase III	Interruption of imatinib in non-progressing patients with GIST was associated with rapid disease progression, resistance to imatinib, and diminished overall survival during long-term follow-up, in contrast to the continuance of imatinib after 3 and 5 years of treatment.	September, 2024	NCT00367861	[94]
2.	Imatinib, 400 mg once daily, oral/ nilotinib, 400 mg twice daily, oral	To assess the efficacy and safety of nilotinib compare to imatinib as first line therapy for GISTs treatment.	Nilotinib impedes the discoidin domain receptor, platelet-derived growth factor receptors (PDGFRs), and ABL1/BCR-ABL1 of TKIs.	A randomized, open-label, multicentre trial with 18 years or older subjects. The subjects with previously untreated, histologically confirmed, metastatic or unresectable GISTs were confirmed for this study. The study confirms the results via progression-free survival as primary and intention-to-treat as secondary endpoints.	Phase III	• In the imatinib group, the most predominant grade 3-4 adverse events included hypophosphatemia, anemia, abdominal pain, and elevated lipase levels. • The most typical adverse events in the nilotinib group were anemia, elevated lipase level, elevated alanine aminotransferase concentration, and abdominal pain. • The predominant serious adverse event observed in both groups was abdominal pain, occurring in 11 participants (4%) in the imatinib group and 14 participants (4%) in the nilotinib group. • The study concluded that nilotinib is not advisable for widespread application in the first-line treatment for GIST.	May, 2015	NCT00785785	[95]
3.	Dasatinib, 70 mg twice daily, Oral	To evaluate the survival rate and tumor response via dasatinib in GIST patients in noncontrolled clinical trial.	TKIs	A single-arm clinical trial with age of patients 13 years or older with measurable imatinib-refractory metastatic GISTs treated at 14 sarcoma referral centers. The patients were accessed for survival for 5 years	Nonrandomized trial	• The primary endpoint was the 6-month progression-free survival (PFS) estimate, with more significant than 30% indicating an active drug and less than 10% indicating an inactive treatment. • The estimated 6-month PFS rate was 29% in the overall population and 50% in a subset of 14 patients with pSRC in GISTs.	April, 2018	-	[96]

(*Continued*)

Table 2

(Continued).

S. No.	Therapeutic intervention, dose, route of administration	Study description/ objective	Mechanism of action	Method	Trial status	Results/outcome in targeted therapy	Year of publication	Trial registration No.	References
				and tumor imaging, response, etc., were accessed. The proto-oncogenes, and platelet-derived growth factors were accessed.		• Dasatinib may exhibit efficacy in a distinctive subset of patients with imatinib-resistant GISTs.			
4.	Dasatinib, 50 mg twice a day for 2 weeks, Oral	To understand the efficacy of Dasatinib oral administration as an alternative therapeutic in advanced GIST treatment.	Inhibition of BCR-ABL1 proteins.	A single-arm multi-centre trial with the enrollment of patients aged 18 years and older with advanced GIST with no prior history of imatinib and sunitinib treatment. RECIST-based progression-free survival (PFS), and response rate, overall survival, etc., have accessed as primary and secondary endpoints.	Phase II	• Patients with wild-type GIST exhibited a longer PFS of 5.5 months. Among four patients with the PDGFRA D842V mutation, two exhibited stable disease. The median overall survival was 14 months. • The most typically documented grade 3 adverse events were anemia and diarrhea.	January, 2019	NCT02776878	[97]
5.	Imatinib, 400 mg daily for 2 years, Oral	To evaluate adjuvant imatinib versus no further therapy after R0-R1 surgery in GIST.	TKIs	A randomized, open-label, multi-center trial conducted in 112 hospitals in 12 different countries. Primary endpoints include failure-free survival (IFFS), whereas, secondary endpoints include toxicity, relapse-free survival (RFS), overall survival (OS), relapse-free interval (RFI).	Phase III	• Imatinib adjuvant treatment for 2 years considerably improved RFS and trended toward greater failure-free survival. • In the high-risk subgroup, imatinib treatment improved long-term IFFS after 9.1 years. While not statistically significant, the difference supports the Scandinavian/German trial's findings of a sustained small but significant long-term OS benefit in high-risk GIST patients treated with 3 years of adjuvant imatinib.	January, 2021	-	[98]

matter[92]. Additionally, the understanding of GIST biology has made this tumor a paradigm for molecularly targeted therapy in solid tumors, providing informative insights into the advantages and limitations of targeted therapeutics[93]. So, it can be concluded that, future medical therapy for GISTs must be focused on addressing treatment resistance, exploring novel therapeutic targets, and developing alternative treatment options beyond the direct inhibition of KIT. The multidisciplinary approach, ongoing research, and collaborative efforts are essential for advancing the management of GISTs and improving patient outcomes.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author contribution

H.S.: conceptualization, data curation, formal analysis, writing - original draft, writing - review and editing; S.M.: data curation, formal analysis, writing - original draft, writing - review and editing, visualization, resources; H.C.: formal analysis, writing - original draft, writing - review and editing, resources; S.C.: formal analysis, writing - original draft; A.K.M.: formal analysis, writing - original draft, writing - review and editing, supervision, resources; T.V.: writing - review and editing, supervision, resources; T.B.E.: conceptualization, data curation, formal analysis, writing - original draft, writing - review and editing.

Conflict of interest disclosure

All the authors declare to have no conflicts of interest relevant to this study.

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