Role of Imatinib in Treatment of GIST

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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.
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Key words: Imatinib, treatment, GIST

1. 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 %) [(1)].

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 [(2)].

Approximately, 75 % of patients with GIST have mutations in the receptor tyrosine kinase KIT (CD117) that lead to KIT over expression. 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 [(3)].

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 [(2)].

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 a very high risk intra-abdominal dissemination and recurrence. Because GISTs rarely metastasize to lymph nodes, formal lymphadenectomy is not necessary [(4)].

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. Imatinibmesylate 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 [(5)].

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 [(6)].

In patients with advanced disease resistant to Imatinib, sunitinib is a safe and effective second line agent [(7)].

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 [(8)].

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.

2. Materials and Methods

We performed 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. According to International committee of medical journal association (ICJME), reviewers must report their findings according to each of the items listed in those checklists [(9)].

Study Selection and Eligibility Criteria:

The present review included studies that fulfilled the following criteria:

1. Studies that included adult patients with gastrointestinal stromal tumors (GIST).
2. Studies that assessed the efficacy and safety of Imatinib at a dose of 400 mg/day for 1 year after surgery in patients with GIST;
3. Studies that compared Imatinib with surgery alone or other treatment modalities;
4. Studies that reported any of the following outcomes: progression-free survival, recurrence-free survival, overall survival, and safety outcomes.
5. Studies that were randomized controlled trials (RCTs) or quasi-randomized studies.

We excluded studies with in any language other than English, studies that did not contain sufficient raw data for estimating an odds ratio (OR) with 95% confidence intervals (CIs), thesis, conference papers, and review articles.

Search Strategy and Screening

An electronic search was conducted from the inception till March 2019 in the following bibliographic databases: Medline via PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science to identify relevant articles. We used different combinations of the following queries: ("Gastrointestinal Stromal Tumors"[Mesh]) AND "ImatinibMesylate"[Mesh]. The search have been done with no limit regarding the year publication.

Screening:

Retrieved citations were imported into EndNote X7 for duplicates removal. Subsequently, unique citations were imported into an Excel sheet and screened by two independent reviewers; the screening was conducted in two steps: title and abstract screening, followed by a full-texts screening of potentially eligible records.

Data Extraction:

Data entry and processing were carried out using a standardized Excel sheet and reviewers extracted the data from the included studies. The extracted data included the following domains: (1) Summary characteristics of the included studies; (2) Baseline characteristics of studied populations; and (3) Study outcomes.

Dealing with Missing Data:

Missing standard deviation (SD) of mean change from baseline was calculated from standard error or

95% confidence interval (CI) according to Altman (**Altman and Bland**, **2005**).

Data Synthesis:

Continuous outcomes were pooled as mean difference (MD) or standardized mean difference (SMD) using inverse variance method, and dichotomous outcomes will be pooled as odds ratio (OR) using Mantel-Haenszel method. The random-effects method was used under the assumption of existing significant clinical and methodological heterogeneity. We performed all statistical analyses using Review Manager (RevMan) 5.3 or Open Meta-analyst for windows.

Assessment of Heterogeneity:

We assessed heterogeneity by visual inspection of the forest plots, chi-square, and I-square tests. According to the recommendations of Cochrane Handbook of Systematic Reviews and meta-analysis, chi-square p-value less than 0.1 denote significant heterogeneity while I-square values show no important heterogeneity between 0% and 40%, moderate heterogeneity from 30% to 60%, substantial heterogeneity from 50% to 100%. If any trials were judged to affect the homogeneity of the pooled estimates, we planned to perform a sensitivity analysis to assess outcomes with and without the trials that were affecting the homogeneity of the effect estimates.

Assessment of publication biases

We intended to test for publication bias using funnel plots if any of the pooled analysis included more than 10 studies in the review (**Higgins 2011).**

3. Results

1. Characteristics of the included studies

In the present study, we searched Medline via PubMed, SCOPUS, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) from their inception till February 2019. The search retrieved 4587 unique records. We then retained 75 potentially eligible records for full-texts screening. Finally, 10 studies (Total No. of patients =3798) were included in the present systematic review and meta-analysis.

2. Characteristics of The included studies

Ten studies were included in the present study, 5 studies were RCTs, while the rest of the studies were Prospective study with historical controls. Five studies assessed adjuvant imatinib 400mg once daily compared to no treatment, 2 studies assessed imatinib 400mg once versus twice daily in patients with unrespectable or metastatic GISTs, and 3 studies assessed imatinib one year versus three studies. The sample size of the included studies ranged from 71 to 946 patients and the mean follow-up ranged from 36-60 months.

The age of the included patients ranged from 18 – 88 years old and the majority of the patients were males. All included studies included patients with performance status 0-1, except two studies which included with unrespectable or metastatic GISTs. The average tumor size ranged from 9.4 to 13cm and the vast majority of the patients had R0 resected margin.

Five included studies assessed Imatinib 400mg versus no treatment, the overall effect estimates favoured Imatinib 400mg compared to no treatment in term of recurrent-free survival (OR 18.33, 95% CI [5.43, 356.43], p <0.001). There was statistically significant heterogeneity (P =0.03; I^2 =62%) (**Figure 1**).

3. Imatinib 400mg versus no treatment

A. Recurrent-free Survival

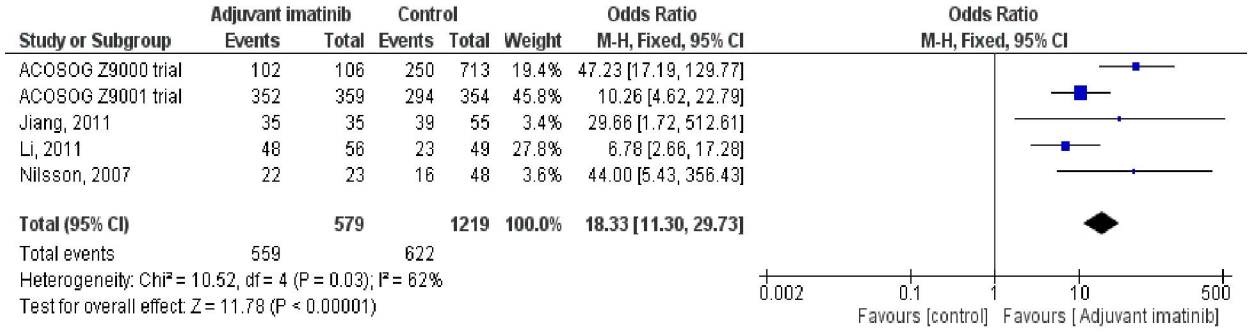

Figure 1: Forest Plot of RFS.

B. Overall Survival

Similarly, the overall effect estimates favoured Imatinib 400mg compared to no treatment in term of overall survival (OR 7.28, 95% CI [5.05, 10.51], p<0.001). There was statistically significant heterogeneity (P =0.001; I^2 =87%) (**Figure 2**).

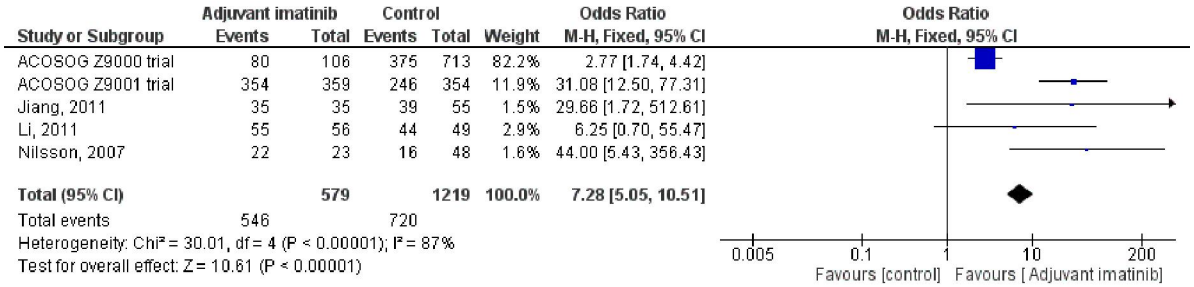

Figure 2: Forest Plot of overall rate of OS.

c. Adverse Events

In terms of safety, the overall effect estimates did not showed significant increases in the risks of grade 1-2 adverse events (OR 0.87, 95% CI [0.63, 1.2], p =0.4). However, grade 3-4adverse events were significantly higher in Imatinib 400mg group (OR 1.71, 95% CI [1.19, 2.46], p =0.004) (**Figure 3**).

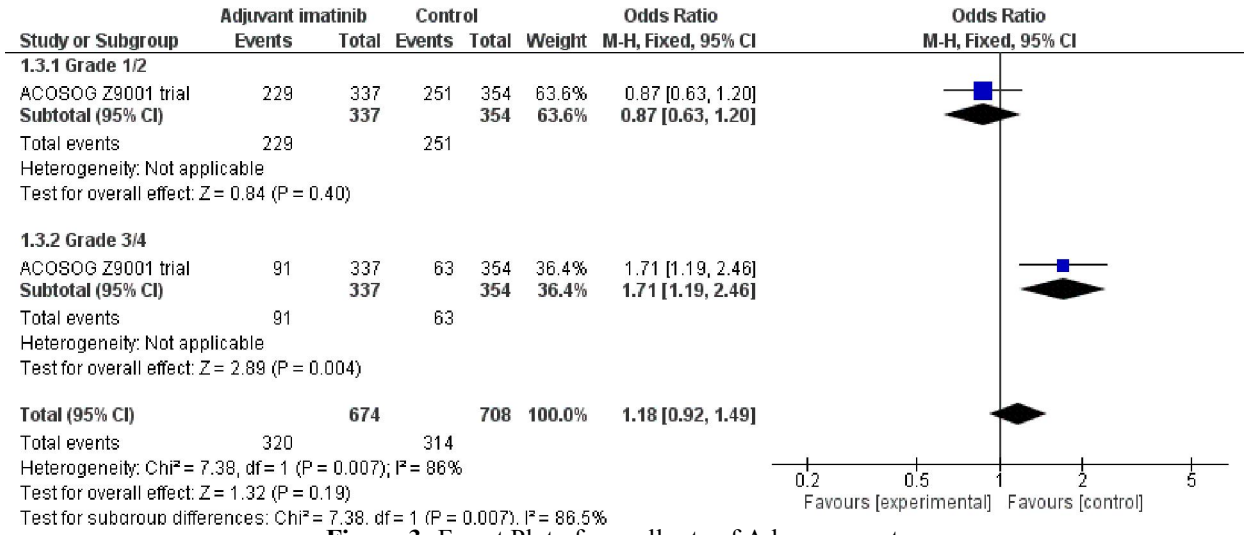

Figure 3: Forest Plot of overall rate of Adverse events.

D. Imatinib One year versus three years

A. Recurrent-free Survival

Three included studies assessed Imatinib for one year versus 3 years, the overall effect estimates favoured Imatinib for 3 years compared to one year in term of recurrent-free survival (OR 2.18, 95% CI [1.64, 2.89], p <0.001). There was no statistically significant heterogeneity (P =0.99; I^2 =0%) (**Figure 4**).

B. Overall Survival

Similarly, the overall effect estimates favoured Imatinib for 3 years compared to one year in term of overall survival (OR 2.44, 95% CI [1.52, 3.91], p <0.001). There was no statistically significant heterogeneity (P =0.74; I^2 =0%) (**Figure 5**).

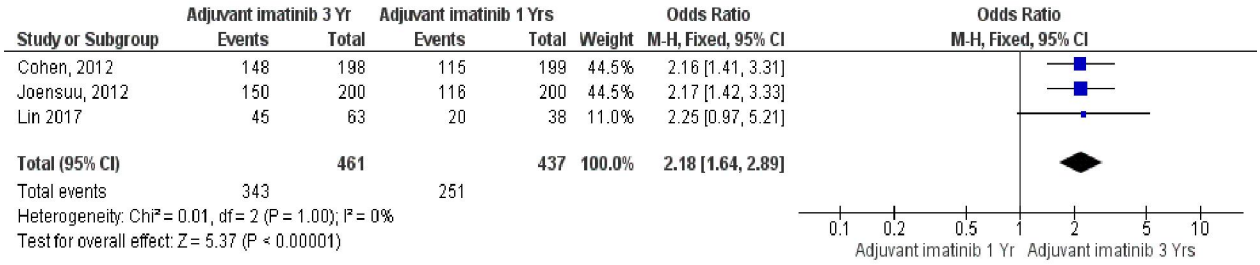

Figure 4: Forest Plot of RFS.

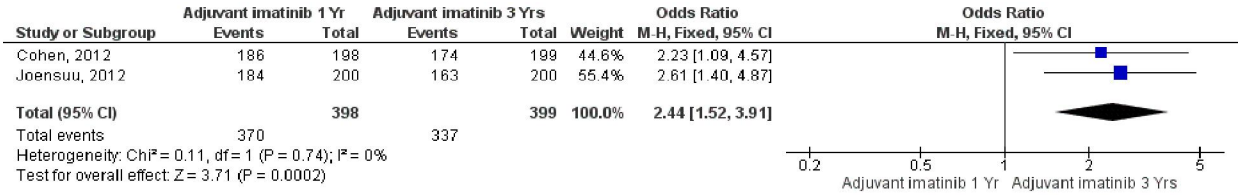

Figure 5: Forest Plot of overall rate of OS.

A. Adverse Events

In terms of safety, the overall effect estimates did not showed significant increases in the risks of grade 1-2 adverse events (OR 0.74, 95% CI [0.52, 1.04], p =0.08). However, grade 3-4adverse events were significantly higher in Imatinib for 3 years compared to one year (OR 0.52, 95% CI [0.38, 0.72], p <0.001) (**Figure 6**).

E. Imatinib 400mg versus 800mg daily

A. Progression-free Survival

B. Two included studies assessed Imatinib 40mmg versus 800mg daily, the overall effect estimates favoured Imatinib 800mg compared to 400mg in term of progressing-free survival (OR 0.54, 95% CI [0.44, 0.66], p <0.001). There was statistically significant heterogeneity (P <0.001; I^2 =96%) (**Figure 7**).

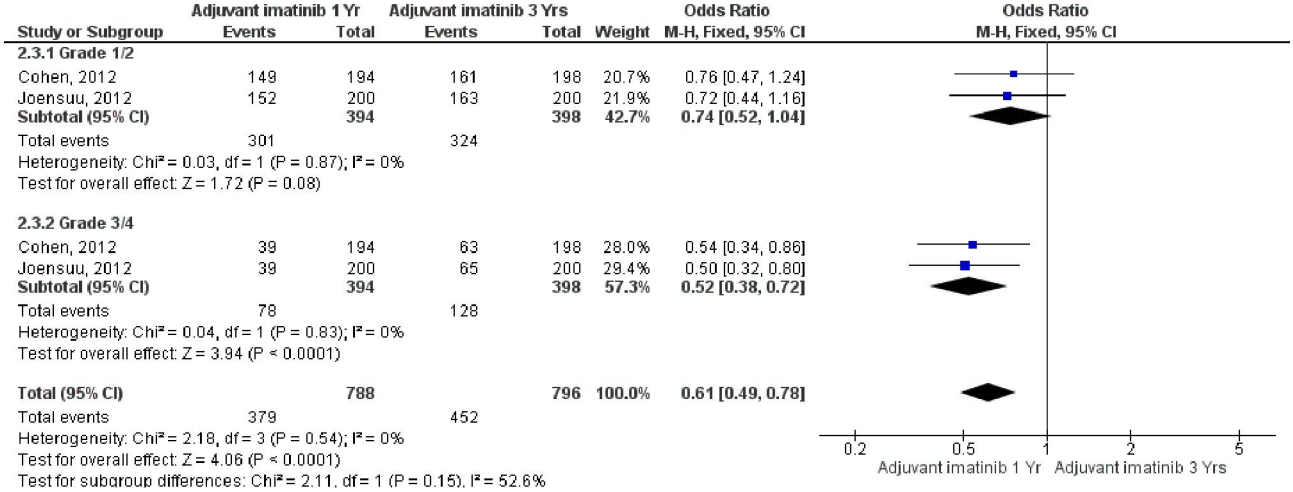

Figure 6: Forest Plot of overall rate of Adverse events.

Figure 7: Forest Plot of PFS.

C. Overall Survival

In contrary, the overall effect estimates did not favoured Imatinib 800mg in term of overall survival (OR 0.84, 95% CI [0.66, 1.06], p =0.15). There was no statistically significant heterogeneity (P =0.02; I^2 =83%) (**Figure 8**).

D. Discontinuation due to Adverse Events

In terms of discontinuation due to adverse events, the overall effect estimates significant increases in the risks of discontinuation rates in Imatinib 800mg arm (OR 0.38, 95% CI [0.29, 0.29], p =0.001) (**Figure 9**).

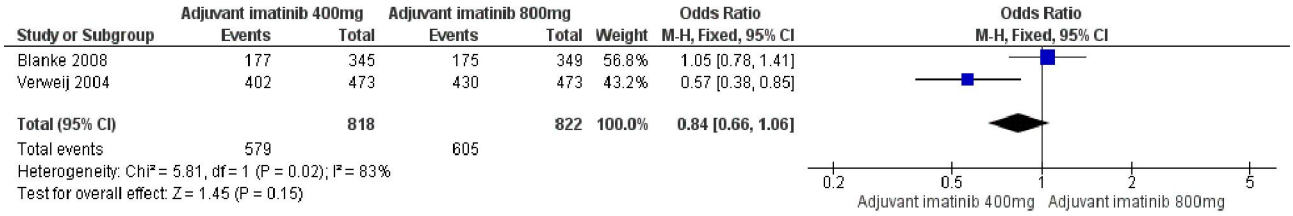

Figure 8: Forest Plot of overall rate of OS

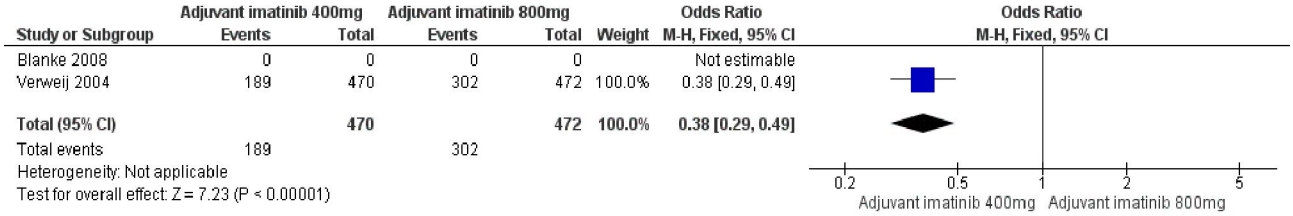

Figure 9: Forest Plot of overall rate of Adverse events.

4. Discussion

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor located in the gastrointestinal (GI) tract. Most studies have reported the incidence of clinically relevant GIST between 10 and 15 cases per million. GISTs are more often located in the stomach (56%) followed by small bowel (32%), colorectum (6%), and esophagus (< 1%). Sporadically, it may affect the omentum, mesentery, and peritoneum. Liver and peritoneum are the most common locations for distant metastases where they appear up to 47% at the time of diagnosis [(10)].

Characteristically, most GISTs (> 95%) are positive for KIT (CD117) protein staining. Approximately 80%-90% of GISTs carry a mutation in the c-KIT gene (80%) or platelet-derived growth factor receptor alpha (PDGFRA) gene, which code for type III receptor tyrosine kinases. Traditionally, GIST tumors have been characterized by their resistance to conventional chemotherapy and radiotherapy treatments. Nevertheless, in 2002, the appearance of the tyrosine kinase inhibitor, Imatinib-Mesylate [(11)].

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. After CML, Imatinib dramatically altered both the management and prognosis for GIST. A number of clinical studies demonstrated the effectiveness of Imatinib in the treatment of unresectable or metastatic GIST. These include studies examining the efficacy and tolerability of different doses of Imatinib (400 mg/day, 600 mg/day, or 800 mg/day) and different dosing regimens [(12)].

Nevertheless, there is still scarcity in the published literature regarding the efficacy and safety of different regimens of Imatinib in GIST. Therefore, we conducted the present systematic review and meta-analysis in order to evaluate the efficacy and safety of adjuvant Imatinib in patients with high-risk GISTs.

In the present study, we searched Medline via PubMed, SCOPUS, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) from their inception till February 2019. A total of 10 studies (Total No. of patients =3798) were included; 5 studies were RCTs, while the rest of the studies were prospective study with historical controls.

The cumulative published evidence suggests that the median age at diagnosis of GIST is 60 years; while there is usually no predilection for either gender but some series suggest a slight male predominance. GIST occurring in the familial form is autosomal dominance. In the present systematic review, the average age of the patients within the included studies ranged from 55-67 years old and there was a slight male predominance in the included studies.

In agreement with our findings, **Søreide and colleagues** [(13)] performed a systematic literature search of all available population-based studies on GIST published between January 2000 and December 2014. The search found 29 studies of more than 13,550 patients from 19 countries that reported sufficient data for regional or national population-based statistics. Age at diagnosis ranged from 10 to 100 years, with the median age being mid 60s across most studies. Gender distribution was equal across studies with slight male predominance.

Ma and colleagues [(14)] utilized a national cancer registry with modern day histological codes to gain greater insight into the true epidemiology of GIST in the United States. The study identified 6,142 patients diagnosed with GIST between 2001 and 2011 in the Surveillance, Epidemiology, and End Results database. The majority of the patients were above 60-

year-olds. GIST was also more common in males than in females.

The standard dose of imatinib for newly diagnosed patients with high-risk GIST is 400 mg daily which represents the first-line therapy with a clinical benefit rate of up to 84%[15]. In the present systematic review and meta-analysis, five included studies assessed adjuvant Imatinib 400mg versus no treatment, the overall effect estimates favored Imatinib 400mg compared to no treatment in term of recurrent-free survival (OR 18.33, 95% CI [5.43, 356.43], p <0.001) and overall survival (OR 7.28, 95% CI [5.05, 10.51], p <0.001).

In concordance with our findings, **Essat and Cooper** [16] performed a systematic review to evaluate the clinical efficacy and safety of imatinib 400mg/day for adjuvant treatment of localized KIT (CD117)-positive resected GIST. Sixteen studies met the eligibility criteria, comprising one randomized controlled trial (RCT), three phase II studies, three cohort studies, and nine case reports. The estimated 1-year recurrence-free survival was 98% [95% confidence interval (CI), 96-100] in the imatinib group versus 83% (95% CI, 78-88) in the placebo group, corresponding to a 65% reduction in the risk of disease recurrence (hazard ratio, 0.35; 95% CI, 0.22-0.53; p < 0.0001) with an absolute recurrence-free survival difference of 15% at 1 year. Other nonrandomized studies reported similar outcomes demonstrating that imatinib used in the adjuvant setting improved recurrence-free survival.

Similarly, **DeMatteo and colleagues** [17]performed a randomized phase 3, double-blind, placebo-controlled, multicenter trial to assess adjuvant treatment with imatinib in localized, primary GIST. From July 2002 to April 2007, 359 patients were randomized to imatinib and 354 to placebo. Imatinib significantly prolonged RFS compared with placebo. Adjuvant imatinib was well-tolerated with a low rate of serious adverse events.

In addition, ACSOG Z9000 was a single-arm, open-label, multicenter, phase II study that recruited patients with primary KIT-positive primary GIST and a high risk for recurrence. Imatinib 400mg /day was given orally for one year, beginning within 84 days of resection. The study indicated that imatinib can prolong RFS and is associated with improved OS compared with historical controls [5].

The efficacy of Imatinib appears to be extended to the unresectable tumor as well. **Cirocchi and colleagues** [18]conducted a systematic review to analyze the role of imatinib mesylate associated with surgery in unresectable and/or metastatic gastrointestinal stromal tumors. In the patients preoperatively treated with Imatinib mesylate, there was a minor incidence of recurrent or metastatic GIST. In this patient group, more complete resections were observed (P = 0.00001). Furthermore, in the same patient group, there was a more significant 12 and 24-month disease-free survival after imatinib treatment and complete resection (respectively P= 0.06 and P= 0.003) and also a better 24-month overall survival (P = 0.004).

On the other hand, the EORTC (European Organisation for Research and Treatment of Cancer) phase I study identified that the highest feasible dose of imatinib to be 400 mg twice daily and indicated extensive activity in GIST. Phase II studies showed activity at all doses tested (ie, 400 to 800 mg) [19]. In the present meta-analysis, we showed that the overall effect estimates favored Imatinib 800mg compared to 400mg in term of progressing-free survival (OR 0.54, 95% CI [0.44, 0.66], p <0.001). However, there was no difference in overall survival (OR 0.84, 95% CI [0.66, 1.06], p =0.15).

In line with our findings, Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST) project conducted a meta-analysis to explore the data of the two large, randomized, cooperative-group studies comparing two doses of imatinib (400 mg daily v twice daily) in 1,640 patients with advanced GIST. At a median follow-up of 45 months, a small but significant PFS advantage was documented for the high-dose arm. OS was identical in the two arms [19].

In addition, **Gronchi and colleagues** [20] conducted a review to evaluatethe use of high-dose imatinib (800 mg daily) in high-risk GIST. Results from published literature showed that patients whose GIST harbors a KIT exon 9 mutation garner a longer progression-free survival time when treated initially with high-dose imatinib (800 mg daily) compared with those patients with KIT exon 11 or no mutations. Thus, the use of high-dose imatinib is recommended by the clinical practice guidelines in these 2 specific clinical situations.

On the other hand, patients with advanced GIST usually respond to imatinib mesylate and other agents that inhibit KIT and PDGFRA, but eventually, most patients have disease progression. Recurrence of GIST is common during the first years following discontinuation of adjuvant imatinib, suggesting that 12 months of administration may be too short a time period. Therefore, it was hypothesized that longer than 1 year of adjuvant imatinib treatment might be beneficial for GIST patients who were considered to have a high risk of GIST recurrence following surgery [21].

In the present meta-analysis, three included studies assessed Imatinib for one year versus 3 years, the overall effect estimates favored Imatinib for 3 years compared to one year in term of recurrent-free survival (OR 2.18, 95% CI [1.64, 2.89], p <0.001)

andoverall survival (OR 2.44, 95% CI [1.52, 3.91], p <0.001).

Similarly, **Joensuu and colleagues** [2] investigated the role of imatinib administration duration as adjuvant treatment of patients who have a high estimated risk for GIST recurrence after surgery. Patients with KIT-positive GIST removed at surgery were randomized Imatinib, 400 mg per day, orally for either 12 months or 36 months, started within 12 weeks of surgery. Patients assigned for 36 months of imatinib had longer RFS compared with those assigned for 12 months and longer overall survival. Imatinib was generally well tolerated.

Conclusion

In conclusion, the present systematic review and meta-analysis showed that adjuvant Imatinib is effective in patients with high risk GISTs, with tolerable safety profile. The meta-analysis results showed that Imatinib significantly improved the overall survival and progression-free survival; and did not increase the risk of severe adverse events. In addition, higher dose (800mg) and longer duration (3 years) of Imatinib appears to be more effective than the standardized regimen. Nevertheless, the currently published literature lacks high quality trials and further studies are still needed to confirm our findings.

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