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Research Article

Follow Up of Metastatic GIST Patients on Targeted Treatments with Abdominal Ultrasound: Reducing Risks without Jeopardizing Survival

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Abstract

Background: The recommended diagnostic procedure for follow-up of metastatic GIST patients on targeted treatments is contrast enhanced CT of the abdomen (ceCTa). It poses several hazards, such as allergic/anaphylactic reactions, kidney damage and radiation exposure. Abdominal Ultrasound (aUS), a much less hazardous diagnostic procedure could be probably used in the follow up of these patients without jeopardizing survival. We report the treatment outcome in metastatic GIST patients with a follow-up protocol incorporating aUS.

Methods: Patients with histologically confirmed, c-kit positive metastatic GIST had before starting imatinib therapy a ceCTa and an aUS and were prospectively followed up every 3-4 months with clinical/laboratory evaluation and an aUS. In case of any abnormality indicating suspected disease progression a ceCTa was performed.

Results: We report the outcome of 81 consecutive patients entered in this protocol from 2001-2011. The median time of follow up was 66 months (maximum 115 months). The median time to progression and overall survival were 52 months (95% CI 42-61) and 72 months (95% CI 64-81) respectively. In average 19, 2 aUS and only 1.7 ceCTa per patient were performed in the follow-up period.

Conclusion: Incorporating an aUS for follow up of metastatic GIST patients treated with targeted therapy could improve their quality of life (less allergic/anaphylactic reactions, less kidney damage, lower exposure to radiation) and reduce health costs without jeopardizing survival.

Keywords: Metastatic GIST; Tyrosine Kinase Inhibitors; Follow-up; Abdominal Ultrasound

Introduction

Gastrointestinal Stromal Tumors (GISTs) are relatively rare neoplasms occurring in the gastrointestinal tract, omentum or mesentery. Complete surgical resection of the tumor is curative, but recurrence of tumors in the liver or peritoneum are common [1]. Unresectable or recurrent tumors do not respond to conventional cytotoxic chemotherapy and are thus associated with poor prognosis. However, the identification of signal transduction pathways associated with the development of GISTs and the use of molecular-targeted therapy with Tyrosine Kinase Inhibitors (TKIs) have yielded remarkable outcomes. In published large series median progression free survival and overall survival of 18-36 months and 48-71 months respectively are reported [2-4]. Adjuvant treatment with imatinib was also investigated and based on these trials [5,6] imatinib is also registered for adjuvant treatment. The prognosis of GIST has therefore, with the introduction of targeted agents changed dramatically and these patients are successfully treated and followed up for a long period of time.

With use of TKIs the classical response criteria (RECIST) were not always found to be useful and different criteria were proposed for treatment evaluation and follow up [7-10]. The standard diagnostic procedure for response evaluation and follow-up recommended by most international clinical guidelines such as ESMO, NCI, NCNN, is besides clinical and laboratory monitoring contrast enhanced CT of the abdomen (ceCTa) every 3-6 months [11-14]. Some reports of contrast enhanced ultrasound are reported in some studies as an early predictor of response to TKI treatment [15]. Although ceCTa is a relatively simple diagnostic procedure, it has several hazards, especially in the context of a regular follow up with relatively short proposed intervals in a disease where we expect survival, times 5, 10 or even more years, especially in case of effective adjuvant treatments. These hazards could be contrast related such as acute and late allergic/anaphylactic reactions in 0, 3% and 14% respectively and contrast induced nephropathy in up to 5% in patients with normal renal function but can be as high as 50% in those with preexisting renal dysfunction [16,17]. Another hazard, somehow neglected in cancer patients, is radiation exposure due to multiple CT procedures. Recurrent ceCTa-s due to cumulative radiation exposure pose a significant Lifetime Attributable Risk (LAR) of radiation-induced

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cancer that correlates with the type and number of CTs performed. Of all diagnostic CTs, ceCTa yields the highest exposure dose, 15mSv [18,19].

Much less hazardous diagnostic procedures as well as less costly, such as abdominal Ultrasound [aUS], could be probably used in the follow up of these patients without jeopardizing survival.

The aim of our report is to present the treatment outcome in metastatic GIST patients with an evaluation and follow-up protocol incorporating aUS.

Methods

The first patient with metastatic GIST starting treatment with imatinib in Slovenia was in November 2001. At that time CT was not easily available in our country as it is today. In order not to compromise the frequency of diagnostic procedures in the follow up of our patients a protocol was proposed by the Institutional Multidisciplinary Sarcoma Board and approved by the Institutional Review/Ethics committee where besides regular clinical and laboratory follow up an aUS was also incorporated. At start of treatment all patients with histologically confirmed, c-kit positive metastatic GIST in the abdomen had a ceCTa and an aUS. They were followed up every 2-3 months with clinical evaluation, laboratory (blood counts, biochemistry) and an aUS every 3-4 months. The abdominal US was performed by an experienced radiologist and each patient was followed up at the same radiology department, if possible by the same radiologist. All abdominal parenchymal organs, retroperitoneum and intraperitoneal space had been checked for pathological lesions, including cysts. Abdominal probes [2-5 MHz] were used. In case of any abnormality indicating suspected disease progression a ceCTa was performed. In all patients the starting dose of imatinib was 400mg/day, in case of documented progression with ceCTa the dose was doubled to 800mg/day and when patients progressed on this dose sunitinib was started at the dose of 37, 5mg/day. Second line treatment with sunitinib was introduced in 2007. Patients with a documented focal progression were operated if that was feasible.

In the 10 years period from November 2001-2011 we treated 81 consecutive patients with TKIs and all are included in the present analysis.

We used the Kaplan-Meier method to calculate the probability of progression free and overall survival from starting treatment with imatinib.

Results

Patient characteristics are listed in (Table 1). The starting dose of imatinib was 400mg/day and due to side effects, mainly hypersensitivity skin reactions, reduced in 20/81 (25%) patients. The median time of follow up was 66 months (maximum 115 months). The median progression free and overall survival was 52 months (95% CI 42-61 months) and 72 months (95% CI 64-81 months), respectively.

In the follow up period disease progression was suspected by aUS in 45/81 patients and confirmed with ceCTa in 39/81 (48%) patients. During the observation period we performed in average 19, 2 aUS and 1, 7 ceCTa per patient. In 8 patients (10%) we detected with our follow up protocol a focal progression and all were operated. Second line treatment with sunitinib (available since 2007) was started in 22 out of the 39 patients progressing on imatinib. Chemotherapy or any other systemic treatments, including treatments within clinical trials, were not used in our patients.

Table 1: Patient characteristics (N=81).

Sex	Male Female	37 (46%) 44 (54%)
Age	Median 63 years	30-86 years
Primary location	Stomach Small bowell Rectum Retroperitoneal and Unknown	39 (48%) 30 (37%) 6 (7,5%) 6 (7,5%)
Site of metastases	Liver Abdominal cavity Liver+Abdominal cavity	31 (38%) 29 (36%) 21 (26 %)

Discussion

Median progression free survival of our metastatic GIST patients treated with TKIs and followed up with a protocol incorporating aUS was 52 months and median overall survival 72 months.

There is a substantial difference if we compare our to the median progression free survival of 18-36 months in our patients to most of the reported studies and series of metastatic GIST patients [2-4]. One probable reason for such long median progression free survival is that we followed-up our patients with a less accurate diagnostic procedure, an aUS and therefore a progression might be detected later, especially when using Choi criteria for identifying focal progression - lesion in a mass with a ceCTa [8-10]. The drawback for not using ceCTa and thus missing disease progression in due time might come from clinical experience from chemotherapy treatment, but this experience can probably not be extrapolated to targeted treatments that have a different mechanism of action. Prolonging the treatment beyond early progression and not changing a treatment that is starting to fail but still slowing the growth rate of the tumor might be an acceptable option maybe even yielding at the end improved survival. This hypothesis is supported by reports in patients with lung adenocarcinoma treated with TKIs [20,21] and as an option of reintroducing imatinib after failure of second/third line treatment in metastatic GIST patients [12]. The second drawback for not using a ceCTa is that we do not identify focal progression early in its course and thus these patients could not be salvaged by a surgical procedure if feasible [22]. But also with our follow-up protocol we detected focal progression in 10% of our patients and all were successfully operated. Another reason for longer progression free survival in our patients could be that a bigger proportion had favorable mutations that have more favorable outcome with longer progression free and overall survival [23]. Since we were not performing routinely a mutation analysis in the past for our GIST patients we have no data to support this hypothesis. A similar approach yielding a high positive predictive value of aUS [82%] compared to ceCTa in the follow-up of testicular cancer patients in detecting liver and retroperitoneal metastases is reported by Murias Quintana et al [24].

With the introduction of targeted treatments survival was substantially improved in metastatic GIST patients when compared to historical controls and is today widely acknowledged as one of the

biggest advances in oncology [25]. Median survival times reported in the largest GIST studies where ceCTa was used to evaluate treatment efficacy and progression at follow up were 57-71 months [2-4]. Although a direct comparison of these median times has no firm scientific value we can nevertheless conclude that with our protocol incorporating aUS in the follow up of these patients their expected median survival time is not compromised.

In the follow-up period of our patients with a median of 66 months we performed in average 19, 2 aUS per patient and only 1.7 ceCTa. In case of standard evaluation and follow-up we would have performed in this period therefore in average 22 ceCTa per patient. This is a significant reduction of the expected incidence of allergic/anaphylactic reactions [16] and kidney damage [17] that both have an important impact on quality of life of these patients as well as costs.

The last but probably not the least important although neglected drawback for using repeatedly a ceCTa is the radiation exposure and Lifetime Attributable Induced Cancer Risk (LAR). According to the recommendations for disease evaluation and follow up (every 3-6 months) each patient undergoes 15-30 ceCTa in 5 years thus exposing him to a radiation dose of 225-450 mSv. For exposures over 250 mSv associated LAR had mean and maximum values of 0.3% and 12% for cancer incidence and 0.2% and 6.8% for cancer mortality respectively [19]. This risk is low and lifetime, but almost one third of these patients [3] have long follow-up and these risks become by time more and more relevant. This problem could be even more important with the introduction of third line treatments, hopefully new treatments in the future and in the follow up of patients after adjuvant treatment.

Conclusion

A protocol incorporating an aUS for treatment evaluation and follow up of metastatic GIST patients treated with TKIs could improve the quality of life of these patients (less allergic reactions, less kidney damage, lower exposure to radiation) and reduce health costs without jeopardizing survival.

Authors' Contribution

BZ participated in the design, coordination of the study, analysis of the data and drafting of the manuscript. SJ participated in the analysis of ultrasound evaluation. MU and EM participated in the collection and analysis of the data and assisted in drafting the manuscript. All authors read and approved the final manuscript.

References

1. Gold JS, Gönen M, Gutiérrez A, Broto JM, García-del-Muro X, Smyrk TC, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol. 2009; 10: 1045-1052.
2. Comparison of Two Doses of Imatinib for the Treatment of Unresectable or Metastatic Gastrointestinal Stromal Tumors: A Meta-Analysis of 1,640 Patients Gastrointestinal Stromal Tumor Meta-Analysis Group MetaGIST J Clin Oncol. 2010; 28: 1247-1253.
3. Blanke CD, Demetri GD, von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol. 2008; 26: 620-625.
4. Yeh CN, Chen YY, Tseng JH, Chen JS, Chen TW, Tsai CY, et al. Imatinib Mesylate for Patients with Recurrent or Metastatic Gastrointestinal Stromal Tumors Expressing KIT: A Decade Experience from Taiwan. Transl Oncol. 2011; 4: 328-335.
5. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, et al. American College of Surgeons Oncology Group [ACOSOG] Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009; 373: 1097-1104.
6. Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial JAMA. 2012; 307: 1265-1272.
7. Hong X, Choi H, Loyer EM, Benjamin RS, Trent JC, Charnsangavej C. Gastrointestinal stromal tumor: role of CT in diagnosis and in response evaluation and surveillance after treatment with imatinib. Radiographics. 2006; 26: 481-495.
8. Benjamin RS, Choi H, Macapinlac HA, Burgess MA, Patel SR, Chen LL, et al. We should desist using RECIST, at least in GIST. J Clin Oncol. 2007; 25: 1760-1764.
9. Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol. 2007; 25: 1753-1759.
10. Choi H. Response evaluation of gastrointestinal stromal tumors. Oncologist. 2008; 13: 4-7.
11. Janine Kalkmann, Martin Zeile, Gerald Antoch, Frank Berger, Stefan Diederich, Dietmar Dinter, et al. Consensus report on the radiological management of patients with Gastrointestinal Stromal Tumours [GIST]: recommendations of the German GIST Imaging Working Group. Cancer Imaging. 2012; 12: 126-135.
12. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23: 49-55.
13. Demetri GD, Benjamin RS, Blanke CD, Blay JY, Casali P, Choi H, et al. NCCN Task Force report: management of patients with gastrointestinal stromal tumor [GIST]--update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw. 2007: 5: S1-29.
14. General Information about Gastrointestinal Stromal Tumors (GIST).
15. Lassau N, Lamuraglia M, Chami L, Leclère J, Bonvalot S, Terrier P, et al. Gastrointestinal stromal tumors treated with imatinib: monitoring response with contrast-enhanced sonography. AJR Am J Roentgenol. 2006; 187: 1267-1273.
16. Pasternak JJ, Williamson EE. Clinical Pharmacology, Uses, and Adverse Reactions of Iodinated Contrast Agents: A Primer for the Non-radiologist Mayo Clin Proc. 2012; 87: 390-402.
17. Loh S, Bagheri S, Katzberg RW, Fung MA, Li CS. Delayed Adverse Reaction to Contrast-enhanced CT: A Prospective Single-Center Study Comparison to Control Group without Enhancement. Radiology. 2010; 255: 764-771.
18. Huda W, He W. Estimating cancer risks to adults undergoing body CT examinations. Radiat Prot Dosimetry. 2012; 150: 168-179.
19. Sodickson A, Baeyens PF, Andriole KP, Prevedello LM, Nawfel RD, Hanson R, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. Radiology. 2009; 251: 175-184.
20. Conforti F, Catania C, Toffalorio F, Duca M, Spitaleri G, Barberis M, et al. EGFR tyrosine kinase inhibitors beyond focal progression obtain a prolonged disease control in patients with advanced adenocarcinoma of the lung. Lung Cancer. 2013; 81: 440-444.
21. Faehling M, Eckert R, Kamp T, Kuom S, Griese U, Sträter J, et al. EGFR-tyrosine kinase inhibitor treatment beyond progression in long-term Caucasian responders to erlotinib in advanced non-small cell lung cancer: a case-control study of overall survival. Lung Cancer. 2013; 80: 306-312.
22. Raut CP, Posner M, Desai J, Morgan JA, George S, Zahrieh D, et al. Surgical

management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. Clin Oncol. 2006; 24: 2325-2331.

23. Heinrich MC, Owzar K, Corless CL, Hollis D, Borden EC, Fletcher CD, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol. 2008; 26: 5360-5367.

24. Quintana EM, Esteban E, López-Muñiz A, Saiz A, Costilla S, Jiménez JR. Abdominal ultrasonography versus abdominal CT in the follow-up of testicular germ cell tumors. Radiologia. 2011; 53: 449-455.

25. Lemonick MD, Parka A. New hope for cancer. TIME Magazine. 2001; 157: 21.

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