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Original Article

Comparison of performance of various tumor response criteria in assessment of sunitinib activity in advanced gastrointestinal stromal tumors☆,☆☆

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ABSTRACT

Purpose: To compare the performance of various tumor response criteria (TRC) in the assessment of patients with advanced gastrointestinal stromal tumor (GIST) treated with sunitinib after failure of imatinib.
Methods: Sixty-two participants with advanced GIST in two clinical trials received oral sunitinib after prior failure of imatinib (median duration 24 weeks; interquartile range 14–56) and were followed with contrast-enhanced computed tomography at baseline and thereafter at median intervals of 6 weeks (IRQ 6–9). Tumor response was prospectively determined using Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, and retrospectively reassessed for comparison using RECIST 1.1, Choi criteria, and modified Choi (mChoi) criteria using the original target lesions. For mChoi criteria, progressive disease was defined as 20% increase in sum of the longest dimension, similar to RECIST 1.1. Clinical benefit rate (CBR; complete response, partial response, or stable disease ≥12 weeks) and progression-free survival were compared between various TRCs using kappa statistics.
Results: While partial response as the best response was more frequent by Choi and mChoi criteria (50% each) than RECIST 1.1 (15%) and RECIST 1.0 (13%), CBR was similar between various TRCs (overall CBR 60%–77%, 77%–94% agreement between all TRC pairs). Time to best response was shorter for Choi and mChoi criteria (median 11 weeks each) compared to RECIST 1.1 and RECIST 1.0 (median 25 and 24 weeks, respectively). PFS was similar for RECIST 1.1, RECIST 1.0, and mChoi (median 35 weeks each), and shortest for Choi criteria (median 23 weeks).
Conclusions: CBR was similar among the various TRCs, although Choi criteria led to earlier determination of disease progression. Therefore, RECIST 1.1 and mChoi criteria may be preferred for response assessment in patients with advanced GIST.

1. Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract [1]. Once considered to have a poor prognosis, management of GIST has been revolutionized by the discovery of the activating mutation of KIT receptor tyrosine kinase and the demonstration of KIT inhibition by imatinib mesylate, a small-molecule tyrosine kinase inhibitor (TKI) [2–4]. Since then, imatinib (Gleevec, Novartis, East Hanover, NJ, USA) and sunitinib (Sutent; Pfizer, New York, NY, USA), both TKIs, have become the standard of care for GIST in the first- and second-line setting, respectively [5–8], and regorafenib (Stivarga; Bayer, Berlin, Germany), a multitargeted TKI acting on KIT and platelet-derived growth factor receptor, is currently used as the third-line agent for TKI-resistant GIST [9,10]. Given the interest in countering secondary mutations which lead to the resistance to TKI therapy, newer second- and later-line agents are being developed. Furthermore, GIST remains the prototype soft tissue tumor for development of targeted therapies based on our improved understanding of intracellular signaling pathways and changes in the radiologic assessment of GIST can possibly also reflect in response assessment of other solid tumors treated with novel therapies.

A multitude of clinical trials for novel anticancer agents have made it necessary to optimize the tumor response assessment utilizing

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standardized tumor response criteria (TRC). Traditionally, treatment response assessment has relied on measurements of tumor size, using World Health Organization criteria [11] and Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [12] and its revised version RECIST 1.1 [13]. However, experience has shown that mere measurement of tumor size is insufficient for response assessment with targeted therapies, leading to the proposal of "morphologic" TRC such as Choi criteria [14], which assess both changes in tumor size and lesion density on computed tomography (CT) imaging. In recent years, however, it has become clear that the novel anticancer agents can cause good response without a significant change in size of the tumor and the lack of significant change in tumor size, that is, stable disease (SD), on TKI therapy in fact represents "clinical benefit." This has led to a paradigm shift in response assessment, and several recent clinical trials now use the term "clinical benefit rate" (CBR) as an outcome measure. [9,15–21]. Therefore, it is important for the radiologists to be aware of this recent terminology (CBR), and the performance of various TRCs and the current utility of "morphologic" TRCs need to be reassessed and validated in the light of CBR.

Despite the availability of multiple TRC, the optimal method of response assessment remains unknown, leading to lack of uniformity in the use of TRCs across clinical trials [7–10,22,23]. With the development of multiple newer agents, there is a persistent need to identify the TRC best suited to assess therapeutic activity in this setting. To address this need, we have previously compared the performance of World Health Organization, RECIST 1.0, RECIST 1.1, and Choi criteria in the assessment of regorafenib activity in patients with advanced GIST after failure of imatinib and sunitinib [24]. We found that while Choi criteria more often showed partial response (PR), the CBR was similar among the various TRCs. Furthermore, progression-free survival (PFS) by Choi criteria was shorter than RECIST 1.0 and RECIST 1.1. This study aims to explore the impact of various TRC on response assessment in patients with GIST treated with sunitinib. Thus, the purpose of this study was to compare the performance of various TRC in assessment of patients with advanced GIST treated with sunitinib after failure of imatinib. We compared the performance of RECIST 1.0, RECIST 1.1, Choi criteria, and modified Choi criteria in terms of CBR [defined as complete response (CR), PR, or SD ≥12 weeks] and PFS.

2. Methods

2.1. Patients

The patients in this study were derived from two separate clinical trials in which patients with pathologically proven advanced GIST and documented failure of previous imatinib therapy were treated with sunitinib [8,25]. Discontinuation of imatinib therapy for at least 2 weeks prior to initiating sunitinib was required for both the trials. Both trials were approved by the institutional review board, and the study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent prior to enrollment into the clinical trial. The current analysis was also approved by the institutional review board.

The first trial was an open-label, single-arm, sequential cohort, dose-escalation phase I and early phase II trial [25]. Sunitinib was administered orally on one of three cyclical treatment schedules: Schedule 2/2 (2 weeks sunitinib and 2 weeks off), Schedule 4/2 (4 weeks on and 2 weeks off), or Schedule 2/1 (2 weeks on and 1 week off). Schedule 2/2 dosing started at 25, 50, or 75 mg/day; Schedules 4/2 and 2/1 started at 50 mg/day. Of total 97 patients enrolled in this trial, 34 patients treated at the Dana-Farber/Harvard Cancer Center who had serial contrast-enhanced CT examinations available for review were included in the present study.

The second trial was a randomized, double-blind, placebo-controlled, parallel-group, multicentre, phase III clinical trial [8]; only patients who received sunitinib were considered for inclusion in the present study. The patients received oral sunitinib on a 4/2 schedule (4 weeks on and 2 weeks off) with a starting dose of 50 mg/day. Dose reductions of sunitinib were required in the case of clinically relevant grade 3 or 4 toxic effects (to 37.5 mg/day and, if additional reduction was warranted, to 25 mg/day), provided criteria for withdrawal from study drug were not met. Of total 312 patients enrolled in this trial from 56 centers in 11 countries, 28 patients treated at the Dana-Farber/Harvard Cancer Center who had serial contrast-enhanced CT examinations available for review were included in the present study.

Thus, our study population comprised 62 patients (44 men, 18 women; mean age 57 years, range 29–75), with the median duration of treatment of 24 weeks [interquartile range (IQR) 14–56 weeks]. Patients received sunitinib until disease progression per RECIST 1.0, the development of unacceptable toxicity, or withdrawal from the study.

2.2. Response assessment

Imaging was performed with CT. At our institution, CT examinations are performed using a 64-detector CT scanner [Somatom Sensation 64 (Siemens Medical Solutions, Forcheim, Germany) or Toshiba Aquilion 64 (Toshiba Medical Systems, Tustin, CA, USA)]. For routine abdominal CT, patients are scanned in the supine position, from diaphragmatic domes to pubic symphysis (0.6- to 1.0-mm collimation, pitch of 0.65–1.00, 120 kVp, and 160–280 mA) and images are reconstructed in 5-mm axial plane and 3 mm in the coronal plane. The examinations are supplemented with oral and intravenous contrast, unless there is a contraindication to intravenous contrast such as a history of severe contrast allergy or renal dysfunction (eGFR ≤30). Only patients who underwent contrast-enhanced CT and in whom the studies were available for review were included in the present study.

Patients enrolled in the first trial underwent imaging at baseline and at the end of every even-numbered cycle [25], while in the second trial, patients underwent imaging at baseline and on day 28 of each treatment cycle [8]. A total of 376 imaging time points were studied; on an average, six imaging time points were available in each patient (range, 2–28). Tumor response was prospectively assessed using RECIST 1.0 at the time of imaging in both the trials [12], using a total of 314 target lesions. The comparative assessment by RECIST 1.1 (total 193 target lesions) [13], Choi criteria (total 193 target lesions) [14], and modified Choi criteria (total 193 target lesions) was retrospectively performed using the same target lesions. For the purpose of this study, modified Choi criteria were defined using a combination of the RECIST 1.1 and Choi criteria: the definition of CR, PR, and SD was the same as original Choi criteria, while progressive disease (PD) was defined as 20% increase in sum of longest dimension, similar to RECIST 1.1 [13,14]. For patients who had more than five target lesions, total or more than two target lesions in a single organ originally selected for RECIST 1.0 criteria, for assessment with RECIST 1.1, Choi criteria, and modified Choi criteria, maximum two target lesions per organ and total up to five target lesions per patient were randomly selected prior to performing any measurements. For Choi and modified Choi criteria, density changes were measured on the same 193 target lesions selected for RECIST 1.1 assessment. Once target lesions were chosen, the same dimensions were used for all TRCs to avoid measurement bias. All the measurements were performed by a single cancer imaging fellowship-trained radiologist with 9 years of experience; the radiologist was blinded to all the clinical information except the diagnosis of GIST.

2.3. Statistical analysis

CBR was defined as the proportion of patients demonstrating CR, PR, or SD ≥12 weeks; this period was chosen based on the available follow-up period in the study cohort. PFS was defined as interval from the date of initiation of drug to the date of disease progression or death, whichever occurred first. PFS and 95% confidence interval (CI) for PFS were