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Adherence to imatinib therapy in patients with gastrointestinal stromal tumors

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ABSTRACT

Imatinib mesylate, an oral tyrosine kinase inhibitor, is indicated for first-line treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumors (GIST). Imatinib also is approved as adjuvant therapy for patients following resection of primary GIST. Despite the efficacy of imatinib for the treatment of patients with GIST, adherence to treatment can prove difficult.

Clinical studies have identified a number of factors that have a significant association with non-adherence to therapy, including age >51 years, female sex, a high number of concomitant medications, and complications with patients' therapy or the disease itself. Moreover, treatment-related adverse events and increased healthcare costs have been shown to have an impact on patients' adherence to therapy. A study of perceptions of adherence to therapy found discrepancies between actual and perceived adherence rates; both patients and physicians overestimate adherence to treatment.

Non-adherence to treatment is not exclusive to oncology, and occurs in other disease areas, particularly with chronic conditions. Evidence from other disease areas suggests that routine assessment of adherence and the implementation of adherence programs can lead to improvements in health status and reduced healthcare costs.

Improving patient adherence to imatinib treatment for patients with unresectable/metastatic GIST is particularly important, because non-adherence has a significant impact on clinical outcomes and healthcare costs. Therefore, the effective management of treatment-related adverse events along with patient education may be important in keeping patients compliant with continuous therapy.

Introduction

Tyrosine kinases are key targets in oncology, as they play an important role in the modulation of growth factor signaling. Imatinib mesylate is an oral inhibitor of the KIT and platelet-derived growth factor receptor-α 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 protuberans [1–3]. 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 [4].

Imatinib is generally well tolerated. Most adverse events are manageable and are often transient or self-limiting [5,6]. The adverse events commonly experienced include nausea and vomiting, diarrhea, musculoskeletal complaints, skin rash, fatigue, hemorrhage, edema, and hematological toxicity [5]. 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.

Adherence to imatinib by patients with GIST in both the adjuvant and metastatic settings can be difficult to achieve, not only because of unwelcomed adverse events, but also as a result of the requirement for long-term continuous daily self-administration [7]. Adherence to imatinib may be further limited in patients with advanced or metastatic GIST, because a clinical response is often achieved rapidly, giving patients a sense of well-being and the impression that stringent adherence to therapy is no longer necessary. In the adjuvant setting, adherence to imatinib may be even more difficult, as patients receiving adjuvant imatinib often do not experience disease symptoms after tumor removal. In the Scandinavian Sarcoma Group/Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie (SSGXVIII/AIO) trial, 12.8% and

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25.8% of patients assigned to receive 12 months or 36 months of adjuvant imatinib, respectively, discontinued the imatinib treatment in the absence of tumor recurrence [7]. In this study, patients with histologically confirmed KIT-positive GIST with a high risk of recurrence according to the modified National Institutes of Health consensus criteria [8] (tumor size >10 cm or tumor mitosis count >10/50 high power field or tumor >5 cm and mitosis count >5/50 high power field or tumor rupture spontaneously or at surgery) received adjuvant imatinib 400 mg daily for 12 or 36 months. The dose of imatinib could be reduced to 300 mg/day if Grade 3/4 non-hematological toxicity occurred or if Grade 2 non-hematological or Grade 3/4 hematological toxicity recurred [7]. Recurrence-free survival and overall survival were significantly better following 36 months of adjuvant imatinib compared with 12 months (Fig. 1) [7]. Given these results, the National Comprehensive Cancer Center guidelines now recommend that postoperative imatinib for at least 36 months should be considered for patients with high-risk GIST, [9] and European Society for Medical Oncology consensus guidelines recommend adjuvant imatinib for 3 years' duration as a standard of care in high-risk operable GISTs [10]. Providing patients with information about the benefit of long-term treatment may help them make treatment decisions that could lead to improved overall survival.

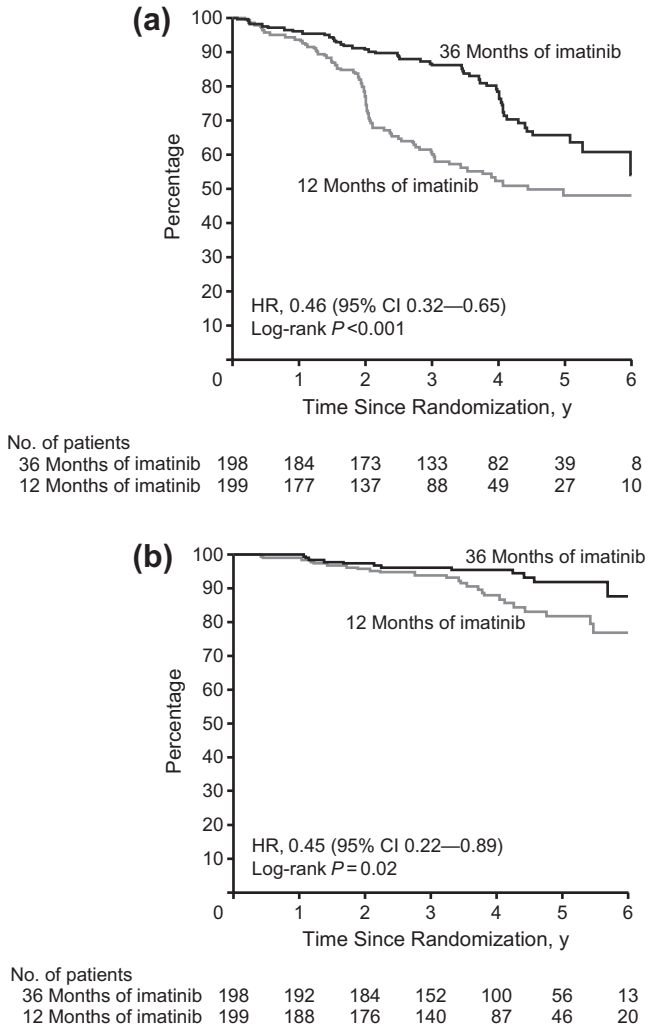

Fig. 1. Scandinavian Sarcoma Group/Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie (SSGXVIII/AIO) trial: (a) recurrence-free survival and (b) overall survival after treatment with imatinib for 12 and 36 months [7].

Economic factors also may affect adherence to imatinib in patients with GIST [11,12]. In an analysis of a nationally representative pharmacy claims database that included patients with Medicare and commercial insurance for whom oral therapy for cancer was initiated between 2007 and 2009, the following factors were seen to be associated with a higher abandonment rate ($P < 0.05$): high cost sharing, increased prescription activity, lower income, and Medicare coverage [12]. In the study, abandonment was defined as reversal of an adjudicated pharmacy claim without a subsequent paid claim for any oral or intravenous cancer treatment within the subsequent 90 days [12].

This review will discuss the role of imatinib in the treatment of GISTs and the issues relating to patient non-adherence. There is a spectrum of patient adherence to therapy, and it is a logical and reasonable interpretation of this spectrum that lower levels of adherence may result in worse clinical outcomes. The implications of non-adherence to imatinib therapy both in terms of deterioration of clinical outcomes and consequent increased healthcare costs are examined, as are practical approaches that may be used to help improve adherence to imatinib in patients with GIST.

Adherence to imatinib in patients with GIST

Data from clinical studies that evaluated adherence and factors associated with non-adherence to imatinib therapy in patients with GIST have shown that suboptimal compliance and persistency with imatinib is a significant problem. However, all these analyses of adherence to therapy were performed in metastatic/advanced setting of GIST therapy, and compliance could be even less favorable when adjuvant therapy is used.

In a retrospective study by Tsang et al., prescription compliance and persistency of patients receiving imatinib for GIST and CML were measured using an analysis of patients' pharmacy claims [13]. Prescription-filling activity for 4043 patients was compared with the prescribing activity for their 3316 physicians, based on pharmacy records accrued over 24 months. Overall compliance was 75% (73% for the GIST patients and 78% for the CML patients). The greatest level of compliance among GIST patients (77%) was found in those initially treated with imatinib 300 or 400 mg/day [13]. Overall persistency (time on therapy without significant gaps in refills) over 24 months was an average of 255 days. Patients who were initially given 300 or 400 mg/day imatinib were the most persistent, with an average of 13.0 and 12.9 months on therapy, respectively [13].

In another retrospective study, [14] claims data from a US health plan were used to identify 413 patients treated with imatinib for CML or GIST who had continuous pharmacy and medical benefits in the 3 months prior and 12 months following, initiation of imatinib. Compliance was defined by medication possession ratio (MPR; total days supply of imatinib in the first year divided by 365). Compliance with imatinib therapy (mean MPR) was 76%, with 30% of patients interrupting therapy for at least 30 consecutive days in the first year [14]. Several factors were identified as having a significant association with non-adherence, including increasing age (>51 years), sex (female), a high number of concomitant medications, and complications with the patient's therapy or the disease itself [14].

In the prospective Adherence Assessment with Glivec: Indicators and Outcomes (ADAGIO) study, the prevalence and severity of non-adherence to imatinib in patients with GIST and CML were investigated during a 90-day period [15]. In a subsequent subanalysis of the data from 28 patients with GIST, [16] the Basel Assessment of Adherence Scale (BAAS) was used to determine actual adherence behavior in the preceding 4 weeks. Of these 28 patients, 23 (82.1%) were receiving adjuvant therapy and the remainder