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Review

Risk stratification models and mutational analysis: Keys to optimising adjuvant therapy in patients with gastrointestinal stromal tumour

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Abstract Imatinib is a standard of care in the adjuvant treatment of patients with resected gastrointestinal stromal tumour (GIST). Two important trials have shown a reduction in GIST recurrence rates for patients treated with imatinib 400 mg daily for 1 year; one of these trials also demonstrated a significant improvement in overall survival for patients with GIST at high risk of recurrence who were treated for 3 years. However, not all patients will benefit from adjuvant treatment. Considering the patient types in both trials, treatment decisions must take into account a number of factors including risk of recurrence and mutational status. Tumour characteristics including tumour size, location and mitotic index are the main prognostic factors of recurrence-free survival (RFS) after surgical resection of GISTs. Research, much of it in the advanced/metastatic setting, shows that mutational analysis is definitely predictive of treatment efficacy and probably prognostic of RFS. Patients on imatinib whose tumours harbour mutations in exon 11 of the *KIT* gene tend to have superior RFS compared with patients with exon 9 mutations. In contrast, patients with wild-type GIST often have disease that follows an indolent course and has limited sensitivity to imatinib in most cases. As such, increased use of existing risk-stratification schemes and mutational analysis will be essential for optimising tailored treatment approaches. In this review, the development and prognostic/predictive utility of key risk stratification tools and mutational analysis of GIST are discussed herein with the goal of facilitating adjuvant treatment decisions for patients with GIST.

1. Introduction

Gastrointestinal stromal tumours (GISTs) are sarcomas of the gastrointestinal tract and represent more than 18% of all sarcomas.[1] Determining the optimal use of systemic adjuvant imatinib in the management

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of patients with localised, resectable GIST is an important goal.

Adjuvant treatment with imatinib for GIST patients was examined in two key trials. In the American College of Surgeons Oncology Group (ACOSOG) randomised, double-blind, Phase III Z9001 study,[2] treatment with 12 months of imatinib was compared with placebo, following complete resection of a primary GIST >3 cm. Primary and secondary end-points were recurrence-free survival (RFS) and overall survival (OS), respectively. Results showed a significant benefit in RFS, but not OS, with 12 months of imatinib. Based on these results, imatinib for the adjuvant treatment of adult patients following resection of KIT-positive GIST was approved by the US Food and Drug Administration (FDA) in 2008 and by the European Medical Agency (EMA) in 2009.

A more recent study conducted by the Scandinavian Sarcoma Group (SSG) and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie (AIO; SSGXVIII/AIO trial) compared 12 versus 36 months of 400 mg/day adjuvant imatinib in patients with GIST at high risk of recurrence (defined as a GIST tumour diameter >10 cm, or mitotic count greater than 10/50 high-powered fields [HPF], or tumour diameter >5 cm and mitotic count greater than 5/50 HPF or tumour rupture).[3] Results showed that both RFS and OS significantly improved with 36 months of imatinib: the 5-year RFS rates for patients receiving 36 versus 12 months of imatinib were 65.6% versus 47.9%, respectively, and the 5-year OS rates were 92% versus 81.7%, respectively.

The National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology now recommend that imatinib be considered for patients at intermediate or high risk of recurrence post-resection, and that at least 36 months of adjuvant imatinib be considered for patients at high risk of recurrence.[4,5] Further, both the FDA and EMA updated the label, extending the duration of adjuvant therapy to at least 36 months in patients at high risk of recurrence.[6] Whether longer treatment durations may be of further benefit is still an open question, which will be addressed by future studies although, paralleling what is commonly done in the metastatic setting, many investigators believe that even adjuvant imatinib should become a chronic therapy. While moving towards more prolonged adjuvant treatment durations, it is all the more essential to identify the appropriate patients to treat in order to avoid the burden of adverse events, or increased financial liability, for those patients who will not derive therapeutic benefit from imatinib.

As alluded to above, risk stratification based on patients' risk of recurrence is a key component to optimising adjuvant treatment. GIST typically recurs in approximately 50% of patients; of high-risk patients, half recur within the first 2 years post-surgery.[7–9] In the ACOSOG Z9001 trial, 83% of patients in the placebo arm and 91% in the imatinib arm did not experience recurrence within 1 year. Of note, this trial also included patients at low and intermediate risk of recurrence, highlighting the importance of evaluating risk in order to identify those patients who are likely to need a treatment.

The other important aspect is to take into account the genetic characteristics of GIST tumours. In the advanced/metastatic GIST setting, patients with mutations in *KIT* exon 11 typically experience better outcomes compared with patients with mutations in exon 9, especially when the latter are not treated with a higher dose (800 mg instead of 400 mg).[4]

In this review, the utility of existing risk-stratification schemes and the potential of mutational analysis techniques to help optimise adjuvant imatinib treatment for patients with resected GIST are summarised.

2. Assessing the risk of relapse for GIST patients

2.1. Risk-stratification systems

Stratification schemes are routinely used to assess the risk of relapse in patients with resectable GIST. Most risk-stratification systems are based on disease characteristics, such as tumour size, mitotic count, anatomic site and presence of metastases.

One of the earliest risk-stratification schemes for GIST was developed with the National Institutes of Health (NIH) in 2001 and estimates metastatic risk based on tumour size and mitotic count.[10] Lower-risk tumours are categorised by smaller size (<2–5 cm) and low mitotic count (<5/50 HPFs); conversely, intermediate- and high-risk tumours are categorised by a combination of larger tumour sizes (>5 cm to any size) and mitotic counts (>5 mitoses to any number).

The risk of GIST recurrence also varies depending on the location of the primary tumour, with GISTs in the stomach being less aggressive, and small intestine and rectal tumours being more aggressive. Based on these observations, Miettinen and colleagues created the Armed Forces Institute of Pathology (AFIP) risk table, a risk scheme that assigned different levels of risk for gastric and intestinal tumours with data from more than 1800 GIST patients.[11]

More recently, several alternative risk stratification schemes have been developed. The Memorial Sloan-Kettering Cancer Center sarcoma team, the Spanish Group on Research for Sarcomas and the Mayo Clinic (Rochester) developed a nomogram that could estimate the probability of RFS at 2 and 5 years after surgery for primary GIST.[12] The NCCN has incorporated this nomogram into their clinical practice guidelines. Another nomogram was developed using data from an Italian retrospective analysis of 929 patients with confirmed GIST and long-term follow-up, and considers