Adjuvant therapy in primary GIST: state-of-the-art


1Interdisciplinary Oncology, HELIOS Klinikum Berlin-Buch, Berlin, Germany; 2Department of Medicine, Centre Léon-Bérard, Lyon, France; 32nd Department of Medical Oncology/Theagenion Cancer Hospital, Thessaloniki, Greece; 4Department of Internal Medicine 1/Division of Oncology, Medical University Vienna—General Hospital, Vienna, Austria; 5COTMES (Comité de Tumores Músculo-Esqueléticos), Mallorca, Spain; 6Department of Cancer Medicine, Istituto Nazionale dei Tumori, Milan, Italy; 7Department of Medical Oncology, Bank of Cyprus Oncology Centre, Nicosia, Cyprus; 8Skåne University Hospital and Lund University, Lund, Sweden; 9Department of Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands; 10Medical Oncology Department, Hygeia Hospital, Athens, Greece; 11Department of Medicine, Institut Gustave Roussy, Villejuif Cedex, France; 12Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; 13Medical Clinic III, Ludwig Maximilians University, Munich, Germany; 14Department of Medical Oncology, Erasmus University Medical Center, Rotterdam, The Netherlands; 15Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland

Received 23 December 2011; revised 8 May 2012; accepted 9 May 2012

Background: The management of primary gastrointestinal stromal tumours (GISTs) has evolved with the introduction of adjuvant therapy. Recently reported results of the SSG XVIII/AIO trial by the Scandinavian Sarcoma Group (SSG) and the German Working Group on Medical Oncology (AIO) represent a significant change in the evidence for adjuvant therapy duration. The objectives of this European Expert Panel meeting were to describe the optimal management and best practice for the systemic adjuvant treatment of patients with primary GISTs.

Materials and methods: A panel of medical oncology experts from European sarcoma research groups were invited to a 1-day workshop. Several questions and discussion points were selected by the organising committee prior to the conference. The experts reviewed the current literature of all clinical trials available on adjuvant therapy for primary GISTs, considered the quality evidence and formulated recommendations for each discussion point.

Results: Clinical issues were identified and provisional clinical opinions were formulated for adjuvant treatment patient selection, imatinib dose, duration and patient recall, mutational analysis and follow-up of primary GIST patients. Adjuvant imatinib 400 mg/day for 3 years duration is a standard treatment in all patients with significant risk of recurrence following resection of primary GISTs. Patient selection for adjuvant therapy should be based on any of the three commonly used patient risk stratification schemes. R1 surgery (versus R0) alone is not an indication for adjuvant imatinib in low-risk GIST. Recall and imatinib restart could be proposed in patients who discontinued 1-year adjuvant imatinib within the previous 3 months and may be considered on a case-by-case basis in patients who discontinued within the previous year. Mutational analysis is recommended in all cases of GISTs using centralised laboratories with good quality control. Treatment is not recommended in an imatinib-insensitive D842V-mutated GIST. During adjuvant treatment, patients are recommended to be clinically assessed at 1- to 3-month intervals. Upon discontinuation, computed tomography scan (CT) scans are recommended every 3 to 4 months for 2 years when the risk of relapse is highest, followed by every 6 months until year 5 and annually until year 10 after treatment discontinuation.

Conclusions: Key points in systemic adjuvant treatment and clinical management of primary GISTs as well as open questions were identified during this European Expert Panel meeting on GIST management.

Key words: adjuvant, gastrointestinal stromal tumour, GIST, imatinib, recommendation

introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract, with an incidence of ∼10 cases per million per year [1]. The development of GISTs is largely driven by mutations in the KIT gene and, to a lesser extent, the PDGFRα gene. Thirty to fifty percent of patients with surgically resected primary GISTs relapse within 5 years, and high-risk patients tend to recur even earlier [1–6]. Imatinib is the mainstay of therapy in metastatic GISTs. It is a potent inhibitor of the KIT and PDGFR receptors, which are the main molecular drivers of GIST. Survival outcomes in patients with metastatic GIST have increased ∼3-fold since the introduction of tyrosine kinase inhibitors.
inhibitors and the median survival in advanced disease has extended to 57 months [7]. Patients with a lower tumour volume have been identified as having better outcomes [8]. Imatinib’s efficacy in the metastatic setting provided a clear rationale for its investigation in the adjuvant setting.

While single-arm studies, phase II ACOSOG Z9000 study and others, by design do not provide conclusive evidence on the clinical outcome in the absence of a control arm, authors of these trials have suggested possible clinical benefits of adjuvant imatinib 400 mg/day over a treatment duration of 1 year through 3 years [9–11]. Three large phase III randomised adjuvant trials have been undertaken with results available from ACOSOG Z9001 and SSG XVIII/AIO trials. These have better elucidated the role of adjuvant therapy in GISTs and shed light on the treatment dose, duration and patient stratification for adjuvant therapy.

The ACOSOG Z9001 (n = 713) was the first large randomised, placebo-controlled trial to demonstrate a relapse-free survival (RFS) benefit of adjuvant imatinib 400 mg/day for 1-year duration, reaching its primary endpoint and unblinding treatment in April 2007 [12]. After a median follow-up of 19.7 months, the estimated 1-year RFS was 98% in the imatinib arm compared with 83% in the placebo arm (hazard ratio: 0.35; 95% confidence interval (CI) 0.22–0.53; P < 0.0001) [12]. This resulted in the approval of imatinib 400 mg/day for 1-year duration in patients at significant risk of relapse. Cross-over of patients who progressed on placebo was permitted. A subanalysis on the basis of tumour size demonstrated RFS benefit in all treatment groups. Later subanalyses of the Z9001 trial by mutation subtype showed a statistically significant difference in 2-year RFS favouring the treatment arm for patients with KIT exon 11 and PDGFRA mutations (excluding PDGFRA D842V), but not for wild-type and KIT exon 9-mutated GISTs [13]. In another multivariate analysis, mitotic rate, tumour size, and small bowel location were predictors of RFS [14]. Limitations of these subanalyses include cross-over and small patient numbers in the individual subgroups, and thus further investigations are warranted. Further questions remained regarding adjuvant therapy, such as: Who would benefit most—which risk level and mutational subtypes? What is the impact of adjuvant therapy on secondary resistance, longer term progression-free and overall survival (OS)? Would doses >400 mg/day benefit patients with exon 9 mutations? What is the optimal duration of adjuvant therapy?

The Scandinavian Sarcoma Group (SSG) and the German Working Group on Medical Oncology [Arbeitsgemeinschaft Internistische Onkologie (AIO)] recently reported results of a large randomised, controlled trial (SSG XVIII/AIO trial) comparing adjuvant imatinib for 3 years with adjuvant imatinib for 1 year in patients with: tumor diameter >10 cm or mitosis count >10/50 HPF, or size >5 cm and mitosis count >5/50 HPFs or tumor rupture spontaneously or at surgery [15]. At 5 years of follow-up (median 54 months), 42% of patients in the 1-year treatment group experienced GIST recurrence, compared with 25% of patients in the 3-year treatment group. The RFS of patients (ITT population) receiving 3 years of imatinib therapy versus 1 year was 87% versus 60% at 3 years of follow-up, and 66% versus 48% at 5 years of follow-up (hazard ratio: 0.46; 95% CI [0.32, 0.65]; P < 0.0001). It is worth noting that in both arms, there is a marked increase in GIST recurrences following imatinib discontinuation, introducing the possibility that even longer duration of adjuvant therapy may yield additional clinical benefit. The OS of patients with 3 years of imatinib therapy versus 1 year was 96% versus 94% at 3 years of follow-up and 92% versus 82% at 5 years of follow-up (hazard ratio 0.45; 95% CI 0.22–0.89; P = 0.019). This represents a >50% reduction in the number of patients dying in the 3-year adjuvant therapy arm when compared with the 1-year treatment group (12 versus 25). Compared with 1 year, 3 years adjuvant imatinib improves RFS and OS in this study population. This justifies a revision of the current treatment recommendations for adjuvant therapy in primary GISTs.

The SSG XVIII/AIO trial results represent a significant change in the available data on adjuvant treatment of primary GISTs, requiring consideration by expert medical oncologists across Europe to interpret clinical significance, evaluate implications for clinical practice and update clinical recommendations. A medical oncology meeting on primary GIST management involving 15 leading experts in GIST was organised by two principal investigators of the SSG XVIII/AIO trial and sponsored by Novartis Oncology. Convened in Frankfurt, Germany, on 20 June 2011, the primary aim was to provide clarity on clinical issues in primary GIST therapy to address gaps in the current recommendations. The goals were to formulate clinical opinions regarding the best approach to adjuvant therapy and patient management in primary GISTs and to guide clinical decision-making regarding patient selection, adjuvant therapy duration, impact of mutational analysis, dose of adjuvant imatinib treatment and monitoring and follow-up of primary GIST patients.

**methods**

The authors were selected as a panel of expert medical oncologists from sarcoma research groups and centres of excellence across Europe. All authors convened for a face-to-face meeting to review and discuss the current literature and formulate clinical opinions on state-of-the-art adjuvant therapy in primary GISTs. The experts reviewed all clinical trials available on primary GIST and adjuvant therapy, including early single-arm trials with imatinib 400 mg/day of various durations, acknowledging the flaws in these studies’ designs, and large randomised, controlled trials. The quality of evidence available from randomised, controlled trials, observational studies, clinical practice guidelines, case reports and systematic reviews was considered. All clinical opinions formulated were based on the available data from well-conducted randomised, controlled trials.

**adjuvant therapy in GIST**

Adjuvant imatinib therapy should be considered a standard treatment in all patients with significant risk of recurrence following resection of primary GISTs. Strong evidence from two large randomised, controlled trials demonstrated the RFS benefit of adjuvant imatinib. The SSG XVIII/AIO trial demonstrates OS benefit and confirms the RFS benefit of adjuvant therapy. Adjuvant imatinib was initiated within 3 months after definitive (R0 or R1) surgery in the two randomised clinical trials demonstrating its efficacy. To ensure access to the multidisciplinary expert team, GIST patients should be referred early to a medical oncologist at a sarcoma...
risk stratification

Patient selection for adjuvant therapy should be based on any of the three commonly used patient risk stratification schemes, all of which have been validated: (i) the Armed Forces Institute of Pathology (AFIP) Miettinen Criteria [16] or (ii) the Modified NIH Joensuu Criteria [17], or (iii) the Gold nomogram [18]. The National Institute of Health (NIH) Fletcher Consensus Criteria [19], which do not account for all three parameters (mitotic index, tumour location and tumour size), may also be used.

Physicians should analyse patient risk based upon several factors including tumour location, size and mitotic count. In a multivariate analysis of the ACOSOG Z9001 trial, mitotic rate, tumour size and small bowel location were all independently associated with and were excellent predictors of poor RFS. The Joensuu criteria incorporate tumour rupture as a factor, classifying all patients with rupture as high risk. Several of risk stratification schemes use cut-off points to categorise risk variables, and these are deemed arbitrary. The individual risk associated with at least two of the relevant factors (tumour size and mitotic count) is on a continuum [20]. Thus, a system that treats risk factors as continuous variables may allow more accurate assessment of the risk of an individual patient and stratification of patients eligible for adjuvant therapy [21].

Other factors, such as concomitant disease, age, World Health Organisation (WHO) performance status, patient refusal and mutational status, also influence individual decision-making regarding adjuvant treatment—particularly in intermediate-risk patients, but also in the high-risk group. The patient population of intermediate-risk patients in clinical practice depends on the risk stratification system used. Using the modified NIH classification (Joensuu) criteria, most intermediate-risk patients can be reclassified as either high risk or low risk [21]. This is due to improved differentiation of intermediate-risk patients; many intermediate-risk patients become either high or lower risk when the modified NIH criteria are used circumventing the problem when to treat intermediate-risk patients with adjuvant imatinib [21]. Imatinib for adjuvant treatment is indicated by the European Medicines Agency in patients at significant risk of relapse (Table 1).

R1 patients

The goal of surgery in primary GISTs is complete removal of the primary tumour (R0 resection). Although no formal study demonstrates poorer prognosis or survival outcomes in R1 resected GIST, in a small single-centre retrospective case series recurrence rates were significantly lower in R0 (9.0% versus 27.8%) resected patients [22]. Tumours where only R1 section is feasible are likely high-risk at presentation. R1 surgery alone is not a high-risk feature, hence was not proposed as an indication for adjuvant imatinib in otherwise low-risk patients. The ESMO recommendations on GIST management address re-excision for R1 margins; repeat surgery is a choice that may be made with the patient, provided the original site of the lesion can be found and major functional sequelae are not foreseen [23].

tumour rupture

Given the adverse prognostic feature, one may consider therapy for GIST patients with tumour rupture to be in the metastatic disease setting. Evidence suggests tumour rupture may carry a similar risk of progression as metastatic disease, and could therefore be considered for lifelong imatinib treatment. In a case series, all but one patient with spontaneous tumour rupture (n=16) developed disease recurrence within 19 months of surgery [24]. The experts estimated that GIST patients with tumour rupture have 80% to 100% risk of recurrence. Tumour rupture needs to be well defined to differentiate spontaneous rupture, rupture with peritoneal spilling or rupture into bowel, from a scratch during surgery. Tumour integrity and any rupture should be fully detailed in the surgical report. In any GIST cases where the surgical report is unclear, surgical and medical oncologists should communicate to accurately establish the patient’s risk of recurrence. The experts’ provisional clinical opinion endorsed patients with tumour rupture be started on imatinib and considered for ongoing treatment >3 years.

dosing adjuvant therapy

The approved imatinib dose for adjuvant therapy is 400 mg/day. No clinical trial in the adjuvant setting has investigated any other dose of imatinib. In the metastatic disease setting, evidence supports the dose of 800 mg/day of imatinib in the treatment of patients with KIT exon 9-mutated GIST [15]. Significantly higher response rates and longer progression-free survival are observed at higher doses of imatinib in exon 9-mutated metastatic GIST. The experts suggested that a higher dose of adjuvant imatinib may benefit exon 9 patients. In the absence of clinical trial data on the adjuvant setting, the experts had no uniform opinion on the optimal dose for all GIST patients harbouring an exon 9 mutation. Clinical trials are needed to solve this open issue but may be challenging to complete due to low patient numbers and tolerability of high-dose imatinib.

mutational status

Mutational analysis is highly important to clinical decision-making in all cases of primary GISTs. Although not yet included in any risk stratification system, the mutational status provides prognostic information. Where it is not immediately available, imatinib therapy may be initiated and reassessed upon receipt of results. An imatinib-sensitive GIST may be assumed in cases of tumour response to neoadjuvant imatinib and where mutational analysis is not available. Quality control is critical; some patients in whom no mutation is found may be erroneously classified as wild-type. Centralised laboratories with good quality control should be widely established to provide mutational analysis.

Mutational analysis is required for adjuvant therapy treatment decisions to provide prognostic information and information about tumour sensitivity to imatinib. However, there is insufficient evidence to formulate a clinical opinion on adjuvant therapy treatment based on mutational analysis alone with the exception of PDGFR A D842V mutation. Treatment is not recommended in imatinib-insensitive D842V-mutated GIST, regardless of risk [25].

Adjuvant imatinib treatment may be considered in patients with true wild-type GISTs, i.e. GIST lacking a detectable KIT or PDGFR A mutation.

Table 1. Summary of provisional clinical opinions by risk stratification

<table>
<thead>
<tr>
<th>Risk assessment</th>
<th>Provisional clinical opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk patients</td>
<td>Adjuvant imatinib treatment 400 mg/day for 3 years duration</td>
</tr>
<tr>
<td>Intermediate-risk patients</td>
<td>The evidence on intermediate-risk patients is insufficient to form a clinical opinion</td>
</tr>
<tr>
<td>Low-risk and very low-risk patients</td>
<td>Adjuvant treatment not recommended.</td>
</tr>
<tr>
<td>Tumour rupture</td>
<td>Imatinib treatment &gt;3 years duration in cases of tumour rupture with suspected tumour dissemination</td>
</tr>
</tbody>
</table>
which may be less sensitive to imatinib than most GISTs with a detectable mutation. Cases of neurofibromatosis type 1-associated GIST strongly express KIT, are usually wild-type for both KIT and PDGFRA and usually indolent in nature. Mutational analysis at KIT exon 9 and exon 11 alone is insufficient to conclude that the GIST is wild-type because there may be mutations in other KIT exons, notably in exon 13 or 17, or in PDGFRA exons 12, 14 or 18. The heterogeneous wild-type subgroup may include GISTs with an undetectable mutation, no mutation or a mutation with unknown sensitivity to imatinib; thus the effect of adjuvant imatinib on wild-type GISTs may be variable. While one cannot conclude that adjuvant therapy in cases of wild-type GISTs with high risk yields no benefit, clinical decision-making should be individualised on a case-by-case basis in discussion with the patient (Table 2).

### Adjuvant Therapy Duration

The optimal duration of adjuvant imatinib therapy is not still known. The authors recommend adjuvant imatinib for 3 years of duration as a standard of care in high-risk operable GISTs. The recommendation of 3 years duration of imatinib adjuvant therapy in the GIST is supported by one large randomised trial, demonstrating superiority of 3 years over 1 year in terms of RFS and OS [15].

In GIST cases where preoperative adjuvant imatinib therapy is used for localised disease for the purpose of organ-sparing tumour shrinkage or patient refusal of surgery, the duration of neoadjuvant therapy should be considered as part of the whole adjuvant treatment duration of 3 years.

### Recall of Patients

With the recent approval of 3 years of adjuvant imatinib therapy for significant risk primary GIST, clinicians will face questions regarding resumption of therapy from patients who have recently discontinued adjuvant therapy. The experts considered a variety of relevant clinical evidence to formulate an opinion for these patients in the absence of data. Adjuvant therapy is intended to treat the patient at a time point when the minimum number of cancer cells is present, with the goal of tumour eradication. The risk of recurrence of GIST is greatest during the first 1 to 2 years after adjuvant imatinib discontinuation; restarting therapy during this period may mitigate this risk. Entry criteria to adjuvant clinical trials showing efficacy required patients to start treatment within 3 months after surgery. Additionally, the BFR14 trial showed that patients who discontinued treatment in the metastatic setting and progressed achieved response upon rechallenge with imatinib, although the quality of the response was not fully recovered [26, 27]. The provisional clinical opinion of the panel recommended recall of patients who discontinued within the previous 3 months and restart of imatinib adjuvant therapy, continuing for an overall duration of 3 years. In patients who have discontinued for up to 1 year, treatment restart could be considered on a case-by-case basis in discussion with the patient. After 1 year of discontinuation, most recurrences would have occurred or be in development. Therefore, no additional follow-up or recall was recommended other than continued monitoring for metastatic GISTs, which would indicate extended imatinib therapy.

### Monitoring

GIST patients are recommended to be followed by sarcoma experts in the field of medical oncology at specialised centres of excellence. During adjuvant treatment, patients are recommended to be clinically assessed including blood cell counts and blood chemistry analysis at 1- to 3-month intervals. Both the risk of radiation and the lesser necessity of intensive computed tomography (CT) scans during adjuvant therapy when the risk of progression is low are important considerations. The optimal follow-up schedule is not known. CT or magnetic resonance imaging (MRI) of the pelvis or abdomen to detect recurrence is recommended every 6 months during adjuvant imatinib therapy. Due to the high risk of recurrence following discontinuation of adjuvant imatinib, the provisional clinical opinion on a follow-up schedule is as follows: CT scans are recommended at short intervals, every 3 to 4 months, for a 2-year period after imatinib discontinuation when most relapses occur, every 6 months for the following 3-year period and then annually. The risk associated with radiation exposure from CT scanning is small compared with the risk of GIST recurrence during this period. Recurrence is rare after the 10th year of follow-up [1, 16, 21] and thus, the benefit of CT monitoring decreases with time while the potential harm increases. Although ultrasound may be used to assess for liver metastases, its role is limited because it poorly detects the intra-abdominal metastases common in GISTs. MRI at the same schedule is a good alternative to CT scanning; however, access to MRI is limited. Long-term survival of patients with metastatic GIST is associated with low tumour burden [4], thus regular monitoring and early detection of GIST recurrence is important.

### Blood Level Testing

The panel debated the potential role of blood level testing in GIST for monitoring patients with poor therapeutic response, severe toxic effects, drug–drug interactions and suspected non-adherence. It is advised to ensure patients do not take concomitant medicines that interact with imatinib, altering plasma levels which may reduce treatment benefit or increase toxicity. In correlational studies, imatinib plasma levels have been suggested to be associated with response to treatment and with side-effects in GISTs. An imatinib pharmacokinetic substudy of the B2222 trial divided patients (n = 73) into quartiles by imatinib trough plasma levels (Cmin) [28]. The analysis suggests that patients with plasma imatinib levels <1100 ng/mL have lower response rates (complete or partial response) and a shorter time to disease progression compared to patients with plasma levels >1100 ng/mL. [28]. The findings suggest that a minimal plasma threshold of imatinib is necessary to obtain and maintain clinical response in patients with GISTs [29]. However, there is a wide interpatient variability in imatinib plasma levels. Once correcting for compliance, inpatient variability was low [30]. A recent imatinib PK study on GISTs found no significant correlation between imatinib trough levels with the volume of metastatic liver involvement, and demonstrated ~20% lower imatinib trough levels 6 months after treatment initiation compared with 1 month on treatment [31]. Thus, although toxicity and underdosing are concerns for patients treated with adjuvant imatinib, the results of blood level testing may not affect clinical decision-making. There is insufficient evidence to support routine assessment of imatinib blood levels during follow-up of

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Provisional clinical opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGFRA D842V mutation</td>
<td>Adjuvant imatinib treatment not recommended</td>
</tr>
<tr>
<td>Wild-type gastrointestinal stromal tumours (GISTs)</td>
<td>Adjuvant imatinib may be considered on a case-by-case basis</td>
</tr>
<tr>
<td>KIT exon 11 mutation</td>
<td>Adjuvant imatinib treatment recommended</td>
</tr>
<tr>
<td>All other mutations</td>
<td>Adjuvant imatinib treatment recommended</td>
</tr>
</tbody>
</table>
patients treated with adjuvant therapy. Rather, routine monitoring and close follow-up are recommended to address side-effects and compliance.

tolerability and compliance

Imatinib is generally well tolerated, and side-effects usually occur early during treatment. Virtually all patients taking adjuvant therapy experience some mild side-effects. Interestingly, in the ACOSOG Z9001 trial, 68% of patients on placebo reported grade 1/2 adverse events and remarkably, 18% reported grade 3/4 side-effects on placebo [12]. Patients’ willingness to continue treatment despite side-effects may be lower in the adjuvant setting versus the advanced disease setting, where the disease risk is more immediate and obvious. Patients should be educated on their diagnosis and prognosis and fully informed about the benefits and risk of side-effects associated with adjuvant therapy. Patients need to be informed about treatment purpose and potential RFS and OS benefits, and the risks associated with underdosing, and treatment interruptions. Patients with no side-effects are recommended to be assessed for compliance.

Severe side-effects, grade 3–4, occurred in one-third of patients treated with adjuvant imatinib therapy for 3 years, compared with 20% of patients treated for 1 year (P = 0.006) [15]. Over 3 years, the most frequently occurring adverse events (any grade) were: anaemia (80%) and peribortal oedema (74%), elevated lactate dehydrogenase (60%), diarrhoea (54%), nausea (51%), muscle cramps (49%), fatigue (48%) and leukopenia (47%) [15]. In the SSGXVIII/AIO trial, 25.8% and 12.6% of the patients assigned to the 36-month and 12-month arms, respectively, discontinued imatinib for another reason than GIST recurrence [15].

Most side-effects are manageable with supportive care measures, such as correction of iron, vitamin B12 or folate deficiencies, or erythropoietin/darbepeotin for anaemia; careful use of diuretics for severe peribortal or peripheral oedema; anti-diarrhoeal or anti-nausea medications; and for the treatment of muscle cramps, increasing fluids, calcium and magnesium supplements, quinine sulfate, muscle relaxants or simply warm socks [32, 33]. If necessary, temporary dose interruptions may be performed or patients may be dose-reduced to 300 mg/day for grade 3/4 non-haematological toxicity or for recurrence of grade two non-haematological or grade 3/4 haematological toxicity.

 Patients on adjuvant therapy should be carefully monitored during the entire duration of adjuvant therapy for side-effects and compliance. In one study in the metastatic setting, adherence was as low as 73%, and persistency declined steadily after about 4 months on imatinib therapy [29].

treatment >3 years

The optimal duration of adjuvant therapy in GISTs is not known. There has been speculation that some patient groups may benefit from lifelong therapy. The non-randomised, open-label, multicentre, phase II PERSIST 5 study is evaluating 5 years of adjuvant imatinib in patients at significant risk of recurrence following complete resection of primary GIST (CSTI571BUS282, ClinicalTrials.gov identifier: NCT00867113). The primary end point is RFS, with secondary end points of OS, safety and tolerability. Due to the non-randomised design, interpretation of the results of this trial may be more challenging compared with randomised trials.

 Patients with suspected metastatic disease may be considered for prolonged imatinib treatment beyond 3 years, even if complete surgery seems to have been performed. In addition to most cases of tumour rupture, these may include cases of extra-gastrointestinal GISTs and patients with very large or inoperable tumours. Some extra-gastrointestinal GISTs may be associated with a small undetected primary tumour and might thus be metastases [21, 34, 35].

conclusions

Targeted agents have long revolutionised the treatment of advanced and, more recently, the treatment of primary GISTs. Imatinib 400 mg/day for 3 years duration is the new standard of care in resected primary high-risk GISTs. It was previously debated whether the time to secondary progression upon recurrence might impact the OS benefit of adjuvant imatinib. The SSG XVIII trial results strongly suggest that one cannot ‘catch-up’ on OS benefit lost from a missed opportunity to treat in the adjuvant setting by treating in the metastatic setting.

Greater knowledge of the prognostic factors that affect patients’ response has increased the importance of tailored treatment of individual patients with GISTs. In the adjuvant setting, these should be used to stratify patients based on individual patient risk for selection of adjuvant therapy. The modified NIH criteria to stratify patients may solve a grey area, by clarifying whether an intermediate-risk patient is eligible or ineligible for adjuvant imatinib. Other aspects to consider include individual patient risk factors such as WHO performance status and disease-related factors such as mutational status, neoadjuvant treatment and the surgical history. The evidence for 3 years of adjuvant imatinib combined with the risk of recurrence suggests benefit of recall of patients who recently discontinued adjuvant therapy. Patients require close monitoring during adjuvant treatment for compliance and early identification of side-effects and post-adjuvant treatment for recurrence.

While the optimal duration of adjuvant therapy remains unknown, 3 years is better than 1 in terms of RFS and OS.

acknowledgements

The meeting and preparation of the manuscript were supported by a grant from Novartis Oncology.

funding

Funding for the meeting logistics, medical writing support to document the meeting discussion and editing the manuscript was provided to Science Agency and Network GmbH by Novartis Oncology.

disclosures

PR is conducting a research sponsored by Novartis and is a member of advisory board and speaker’s bureau for Novartis, Pfizer and Bayer. J-YB. has received speaker’s honoraria and financial support for research from Novartis, Pfizer, Roche, GSK and Pharmamar. IB has received speaker’s honoraria from Novartis. TB has received advisory board and speaker’s honoraria from Novartis. PGC has received advisory board, consultancy, speaker’s honoraria from and is involved in clinical trials sponsored by Bayer, Infinity, Novartis and Pfizer. MD has received speakers’ honoraria paid to the Bank of Cyprus Oncology Centre, by Novartis. ME has received advisory board, consultancy and speaker’s honoraria from Novartis. HG’s institution has received research grants for
Novartis. HJ has received financial support for research paid to the Clinical Research Institute of Helsinki University Central Hospital, by Novartis. PK has received advisory board honoraria from Novartis. AL has received speaker’s honoraria from Novartis, Pfizer and Pharmamam. JV has received consultancy honoraria from Novartis. JMB, ALP and MS have no conflicts of interest to disclose.

references


