Annals of Oncology 19 (Supplement 2): ii35–ii38, 2008
doi:10.1093/annonc/mdn080

Gastrointestinal stromal tumors: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

P. G. Casali[1], L. Jost[2], P. Reichardt[3], M. Schlemmer[4] & J.-Y. Blay[5]
On behalf of the ESMO Guidelines Working Group*

[1]*Department of Cancer Medicine, Istituto Nazionale dei Tumori, Milan, Italy;* [2]*Department of Oncology, Kantonsspital, Bruderholz, Switzerland;* [3]*Department of Hematology, Oncology and Palliative Care, Helios Klinikum, Bad Saarow, Germany;* [4]*III Medical Clinic and Polyclinic, Munich, Germany;* [5]*INSERM U590, Claude Bernard University, Lyon, France*

incidence

Gastrointestinal stromal tumors (GIST) are rare tumors, with an estimated incidence of 1.5/100 000/year.

diagnosis

When GIST present as a small esophago-gastric or duodenal nodule ≤2 cm in size, endoscopic biopsy may be difficult, and laparoscopic/laparotomic excision may be the only way to get to a histologic diagnosis. Many of these small nodules are low-risk GIST or other non-malignant entities. Therefore, the standard approach to these patients is endoscopic ultrasound and then follow-up, reserving excision for patients whose tumor increases in size. Alternatively, the decision can be shared with the patient to make a histologic assessment. On the other hand, the standard approach to nodules >2 cm in size is biopsy/excision, because, if GIST, they imply a higher risk. The standard approach to rectal (or recto-vaginal space) nodules is biopsy/excision after ultrasound assessment regardless of the tumor size, because the risk is higher and the local implications for surgery are more critical. However, a follow-up policy may be an option, shared with the patient in the case of small lesions.

If there is an abdominal nodule not amenable to endoscopic assessment, laparoscopic/laparotomic excision is the standard approach. If there is a bigger mass, especially if surgery is likely to be a multivisceral resection, multiple core needle biopsies are the standard approach. This may let the surgeon plan the best approach according to the histologic diagnosis and may avoid surgery for diseases which do not merit it (e.g. lymphomas, mesenteric fibromatosis, germ cell tumors). The risk of peritoneal contamination is negligible if the procedure is properly carried out. Lesions at risk in this regard (e.g. cystic masses) should be biopsied in specialized centers. Immediate laparoscopic/laparotomic excision is an alternative on an individualized basis, especially if surgery is limited.

If a patient presents with conspicuous metastatic disease, then a biopsy of the metastatic focus is sufficient and the patient usually does not require a laparotomy for diagnostic purposes.

The tumor sample should be fixed in formalin (Bouin fixation should be avoided, since it may impair the feasibility of molecular analysis). Frozen tissue collection is encouraged, because new molecular pathology assessments may become available later on and be made in the patient's interest. Appropriate informed consent should be sought to allow for later analysis and further research.

Pathologically, the diagnosis of GIST relies on morphology and immunohistochemistry. CD117 is generally positive, although a proportion of true GIST (in the 5% range) are CD117-negative. Antigen retrieval may result in false positive CD117 staining. Mitotic count has prognostic value, and should be expressed as number of mitoses per 50HPF.

Mutational analysis for known mutations involving KIT and PDGFRA genes can confirm the diagnosis of GIST, if doubtful (particularly in CD117-negative suspect GIST). In addition, mutational analysis has predictive and prognostic value, so that it is strongly recommended in the diagnostic work-up of all GIST. Centralization of mutational analysis in a laboratory enrolled in an external quality assurance program and with expertise in the disease may be useful in order to make mutational analysis more widely available.

staging and risk assessment

The risk of relapse may be estimated on the basis of some prognostic factors, which should be recorded on a standard basis: mitotic rate, tumor size, tumor site, surgical margins (including whether tumor rupture occurred).

Tumor size and mitotic count are considered by the 2002 Consensus risk classification. This was correlated with prognosis in an epidemiological study, showing that the 'high risk' category has a much worse prognosis than the others.

**Correspondence to:* ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland

Approved by the ESMO Guidelines Working Group: February 2008. This publication supercedes the previously published version—Ann Oncol 2007; 18 (Suppl 2): ii27–ii29.

Conflict of interest: Dr Casali and Dr Reichardt have not reported any conflicts of interest; Dr Jost and Dr Schlemmer have reported no conflicts of interest; Prof. Blay has reported that he is currently conducting research sponsored by Novartis, Pfizer, GSK, Pharmamar, Roche and that he received honoraria and research grants from these companies. He also reported that he is a member of the speakers' bureau for Novartis and Pfizer.

'Very low risk' and 'low risk' categories have a very favorable prognosis. The 'intermediate risk' category probably does not discriminate well and includes cases at both low and high risk.

A more recently proposed risk partitioning incorporates tumor site in addition to the mitotic count and tumor size. In particular, it reflects the fact that gastric GIST have a better prognosis than small bowel or rectal GIST. The risk estimate for subgroups is based on a single retrospective analysis, and therefore needs confirmation. However, this classification better distinguishes across different risk levels.

Tumor rupture, whether spontaneous or at the time of surgical resection, should be recorded, because it denotes a highly adverse prognostic value due to peritoneal contamination. However, it is uncertain whether these patients should be considered metastatic. Abdominal washing during surgery may be an option in case of tumor rupture. Careful surgical exploration for small peritoneal nodules is important.

Staging procedures take into account the fact that most relapses affect the peritoneum and the liver. Contrast-enhanced abdominal and pelvic CT scan is of choice for staging and follow-up. MRI may be an alternative. For rectal GIST, MRI provides better preoperative staging information. Chest CT scan or X-rays and routine laboratory testing complement the staging work-up of the asymptomatic patient. Evaluation of FDG uptake using PET scan, or PET–CT/MRI, is useful mainly when early detection of tumor response to imatinib treatment is of special concern.

treatment

Multidisciplinary treatment planning is needed (involving pathologists, radiologists, surgeons, medical oncologists), such as that which is available in referral centers for sarcomas and GIST, and/or within collaborative networks sharing multidisciplinary expertise.

limited disease

Standard treatment of localized GIST is complete surgical excision, without dissection of clinically negative lymph nodes [IV, A]. If laparoscopic excision is planned, the technique needs to follow the principles of oncologic surgery. A laparoscopic approach is clearly discouraged in patients who have large tumors. R0 excision is the goal. If an R1 excision has been made, re-excision may be a choice, provided the original site of lesion can be found and major functional sequelae are not foreseen. When R0 surgery implies major functional sequelae, and preoperative medical treatment has not helped or cannot be foreseen, the decision can be shared with the patient to accept R1 margins, particularly for low-risk lesions, in the lack of a formal demonstration that R1 surgery is associated with a worse overall survival. Patient referral to a specialized center should be considered, and R0 resection should be considered as the reference standard.

If R0 surgery is not feasible, or it might be achieved through less mutilating surgery in the case of cytoreduction, imatinib pretreatment is recommended [IV, A]. This may also be the case if the surgeon believes that the surgical conduct is safer after cytoreduction (e.g. the risk of bleeding and tumor rupture is decreased). Following maximal tumor response, generally after 6–12 months, surgery is performed. Mutational analysis may help to exclude non-sensitive mutations from therapy with imatinib. PET scan, or PET–CT/MRI, may be particularly useful to assess tumor response very rapidly, in terms of a few weeks, so that surgery is not delayed in the case of non-responding disease.

The risk of relapse can be substantial, or relatively high, in many presentations, depending on mitotic count, tumor size and site of disease. Given the efficacy of imatinib in the disease, adjuvant treatment with the drug has been studied. Definitive results are still not available, although an early advantage in relapse-free survival was reported in a preliminary format, with a limited follow-up and number of events, by one randomized study performed in >3 cm localized GIST. The demonstrated benefit is in terms of early relapse-free survival, so that a longer follow-up is needed to draw definitive conclusions, in particular with regard to the absolute relapse rate, the length of the delay in relapse and the behavior of secondary resistance to imatinib in relapsing patients. Overall survival, relapse-free rate at a longer interval, time to secondary resistance are relevant end-points to take into account in clinical studies open to accrual or follow-up. Currently, adjuvant imatinib treatment for GIST patients with localized disease is considered investigational.

extensive disease

In locally advanced inoperable patients and metastatic patients, imatinib is standard treatment [IV, A]. This applies also to metastatic patients who have been completely relieved of all lesions surgically, being discovered unexpectedly.

Standard dose of imatinib is 400 mg daily [I, A]. Data have been provided that patients with exon 9 KIT mutations fare better in terms of progression-free survival on a higher dose level, i.e. 800 mg daily, which is therefore standard treatment in this subgroup [III, A]. Treatment should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumor progression in virtually all cases, even when lesions have been previously surgically excised [II, B]. Dose intensity should be maintained by proper management of side-effects and a correct policy of dose reductions and interruptions in the case of excessive, persistent toxicity. Close monitoring of tumor response should be continued throughout treatment, since the risk of secondary progression persists over time.

Complete excision of residual metastatic disease has been shown to be related to a good prognosis, provided the patient is responding to imatinib, but it is left to be demonstrated whether this is due to surgery or to a selection bias. Therefore, surgery of metastatic responding patients is considered investigational.

The standard approach in the case of tumor progression is to increase the imatinib dose to 800 mg daily [III, B]. This may be useful in case of a KIT exon 9 mutated GIST, if the patient started at 400 mg; probably in case of changes in drug pharmacokinetics over time (which is amenable to assessment and constitutes a subject of study); or, possibly, in case of some secondary molecular alterations. Also patient non-compliance should be ruled out as a possible cause of tumor progression, as well as drug interactions with concomitant medications.

In case of progression or intolerance on imatinib, second-line standard treatment is sunitinib [II, B]. The drug was proved effective in terms of progression-free survival following a '4 weeks on–2 weeks off' regimen. Preliminary data have been provided that a continuous regimen with a lower daily dose may be equally effective and possibly better tolerated, so that this regimen can be an option on an individualized basis.

After failing on sunitinib, the patient with metastatic GIST should be considered for participation in a clinical trial of new therapies or new combinations.

Surgical excision of progressing disease has not been rewarding in published series, but surgery of limited progression, such as the 'nodule within a mass', has been associated with a progression-free interval in the same range as for second-line treatment with sunitinib. Therefore, it may be a palliative option in the individual patient with a limited progression. Non-surgical procedures (local treatment, such as ablations, etc.) may be selected.

There is anedoctal evidence that patients who have already progressed on imatinib may occasionally have a benefit when rechallenged with the same drug. Likewise, maintaining treatment with an anti-tyrosine kinase agent even in the case of progressive disease may slow down progression as opposed to stopping it, of course if no other option is available at the time. Therefore, rechallenge or continuation treatment with an anti-tyrosine kinase agent to which the patient has already been exposed may be an option in individual cases. On the other hand, combinations of anti-tyrosine kinase agents should be discouraged outside of clinical studies, because of the potential for considerable toxicity.

response evaluation

Antitumor activity translates into tumor shrinkage in the majority of patients, but some patients may show only changes in tumor density on CT scan, or these changes may precede a delayed tumor shrinkage. These changes in tumor radiological appearance should be considered as tumor response. In particular, even some increase in tumor size may be indicative of tumor response if tumor density on CT scan is decreased. Even the 'appearance' of new lesions may depend on their being more evident when becoming less dense. Therefore, both tumor size and tumor density on CT scan, or consistent changes on MRI, should be considered as criteria for tumor response. FDG–PET scan has proved to be highly sensitive in early assessment of tumor response, and may be useful in doubtful cases, or when early prediction of response is highly useful (e.g. preoperative cytoreductive treatments). The absence of tumor progression after months of treatment equally amounts to tumor response. On the other hand, also tumor progression may not be accompanied by changes in tumor size. In fact, some increase in tumor density within tumor lesions may be indicative of tumor progression. A typical progression pattern is the 'nodule within the nodule', by which a portion of a responding lesion becomes hyperdense.

follow-up

There are no published data supporting specific policies for follow-up of surgically treated patients with localized disease. Relapses most often occur to the peritoneum or in the liver. The mitotic rate likely affects the speed at which relapses take place. Risk assessment based on mitotic count, tumor size and tumor site may help in choosing the routine follow-up policy. High-risk patients generally relapse within 2–3 years, while low-risk patients may relapse later, although much less likely. That said, routine follow-up schedules differ across institutions. As an example, in some institutions intermediate–high-risk patients undergo a routine follow-up with CT scan every 3–4 months for 3 years, then every 6 months until 5 years, and yearly afterwards; for low-risk tumors, follow-up is carried out with CT scan every 6 months for 5 years. Very low risk GIST probably do not deserve routine follow-up, although one must be aware that the risk is not nil.

authors

These Clinical Recommendations have been formulated following a consensus process based on a consensus event organized by ESMO in Lugano in October 2007 and a manuscript revision taking place thereafter up to January 2008. The consensus process involved experts from the community of the European sarcoma research groups and from some sarcoma centers of excellence outside Europe, indicated hereafter. The text reflects an overall consensus among them, although each of them may not always find it consistent with his/her own views. The EU-funded network of excellence CONTICANET (CONnective TIssue CAncers NETwork) supported the consensus process. The consensus event was made possible financially by unrestricted grants from Novartis Oncology, Pfizer Oncology and PharmaMar.

consensus panel

Paolo G. Casali, Milano, Italy (Coordinating author)
Jean-Yves Blay, Lyon, France (Coordinating author)
Lorenz Jost, Bruderholz, Switzerland (Reviewer)
Peter Reichardt, Berlin, Germany (Reviewer)
Marcus Schlemmer, Muenchen, Germany (Reviewer)
Massimo Aglietta, Torino, Italy
Thor Alvegard, Lund, Sweden
Larry Baker, Ann Arbor, USA
Robert Benjamin, Houston, USA
Martin Blackstein, Toronto, Canada
Sylvie Bonvalot, Paris, France
Ioannis Boukovinas, Thessaloniki, Greece
Binh Bui, Bordeaux, France
Angela Buonadonna, Aviano, Italy
Paola Collini, Milano, Italy
Alessandro Comandone, Torino, Italy
Enrique de Alava, Salamanca, Spain
Maria Debiec-Rychter, Leuven, Belgium
Angelo Paolo Dei Tos, Treviso, Italy
George D. Demetri, Boston, USA
Palma Dileo, Milano, Italy
Mikael Eriksson, Lund, Sweden
Andrea Ferrari, Milano, Italy
Stefano Ferrari, Bologna, Italy
Sergio Frustaci, Aviano, Italy
Xavier Garcia-Del-Muro, Barcelona, Spain

Robert Grimer, Birmingham, UK
Alessandro Gronchi, Milano, Italy
Federica Grosso, Milano, Italy
Pancras Hogendoorn, Leiden, Netherlands
Peter Hohenberger, Mannheim, Germany
Rolf Issels, Munich, Germany
Svetlana Jezdic, Lugano, Switzerland
Heikki Joensuu, Helsinki, Finland
Ian Judson, London, UK
Michael Leahy, London, UK
Serge Leyvraz, Lausanne, Switzerland
Axel Le Cesne, Paris, France
Robert Maki, New York, USA
Javier Martin, Mallorca, Spain
Joan Maurel, Barcelona, Spain
Pierre Meeus, Lyon, France
Michael Montemurro, Lausanne, Switzerland
Patrizia Olmi, Milano, Italy
Shreyas Patel, Houston, USA
Piero Picci, Bologna, Italy
Andres Poveda, Valencia, Spain
Martin H. Robinson, Sheffield, UK
Piotr Rutkowski, Warsaw, Poland
Patrick Schoffski, Leuven, Belgium
Stefan Sleijfer, Rotterdam, Netherlands
Kirsten Sundby Hall, Oslo, Norway
Elena Tamborini, Milano, Italy
Jonathan Trent, Houston, USA
Frits Van Coevorden, Amsterdam, Netherlands
Martine Van Glabbeke, Brussels, Belgium
Allan Van Oosterom, Leuven, Belgium
Jaap Verweij, Rotterdam, Netherlands
Eva Wardelmann, Bonn, Germany
John Zalcberg, Melbourne, Australia

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

literature

1. Benjamin RS, Choi H, Macapinlac HA et al. We should desist using RECIST, at least in GIST. J Clin Oncol 2007; 25: 1760–1764.
2. Blanke CD, Rankin C, Demetri GD et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 2008; 26: 626–632.
3. Blay JY, Le Cesne A, Ray-Coquard I et al. Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. J Clin Oncol 2007; 25: 1107–1113.
4. Debiec-Rychter M, Sciot R, Le Cesne A et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006; 42: 1093–1103.
5. DeMatteo RP, Gold JS, Saran L et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer 2008; 112: 608–615.
6. DeMatteo RK, Owzar KR, Maki R et al. Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumor (GIST): North American intergroup phase III trial ACOSOG Z9001. ASCO Annual Meetings Proceedings Part I. J Clin Oncol 2007; 25 (18 Suppl): 10079.
7. Demetri GD, van Oosterom AT, Garrett CR et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006; 368: 1329–1338.
8. Demetri GD, von Mehren M, Blanke CD et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002; 347: 472–480.
9. Fletcher CDM, Berman JJ, Corless C et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Human Pathol 2002; 33: 459–465.
10. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006; 130: 1466–1478.
11. Novitsky YW, Kercher KW, Sing RF, Heniford BT. Long-term outcomes of laparoscopic resection of gastric gastrointestinal stromal tumors. Ann Surg 2006; 243: 738–745.
12. Raut CP, Posner M, Desai J et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol 2006; 24: 2325–2331.
13. Van Glabbeke M, Verveij J, Casali PG et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organization for Research and Treatment of Cancer – Italian Sarcoma Group – Australasian Gastrointestinal Trials Group study. J Clin Oncol 2005; 23: 5795–5804.
14. Verweij J, Casali PG, Zalcberg J et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatininb: randomized trial. Lancet 2004; 364: 1127–1134.
15. Zalcberg JR, Verveij J, Casali PG et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. Eur J Cancer 2005; 41: 1751–1757.