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

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incidence

Gastrointestinal stromal tumours (GIST) are rare tumours, 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 entities whose clinical significance remains unclear.

Therefore, the standard approach to these patients is endoscopic ultrasound assessment and then follow-up, reserving excision for patients whose tumour 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 tumour 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 tumours). 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 centres. Immediate laparoscopic/laparotomic excision is an alternative on an individualized basis, especially if surgery is limited. If a patient presents with obvious metastatic disease, then a biopsy of the metastatic focus is sufficient and the patient usually does not require a laparotomy for diagnostic purposes. The tumour 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 as long as this is allowed by local and national guidelines.

Pathologically, the diagnosis of GIST relies on morphology and immunohistochemistry. CD117 is generally positive, although a proportion of true GIST (in the 5% range) is 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 50 HPF. 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 value for sensitivity to imatinib 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.

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Conflict of interest: Dr Casali has reported that he received honoraria and travel coverage for medical meetings from Novartis; he had a consultancy role with Infinity Pharmaceuticals and he had an unremunerated consultancy role with Pfizer; he is currently conducting research sponsored by Novartis, Pfizer and Infinity Pharmaceuticals. Dr Jost has reported no conflicts of interest. Dr Reichardt has not reported any conflicts of interest. Dr Schlemmer has 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 has also reported that he is a member of the speakers' bureau for Novartis and Pfizer.

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, tumour size, tumour site, surgical margins (including whether tumour rupture occurred). Tumour 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. 'Very low risk' and 'low risk' categories have a very favourable prognosis. In most of the population-based series, the 'intermediate risk' category of the Consensus classification did not discriminate patients with an unfavourable prognosis.

A more recently proposed risk partitioning incorporates tumour site in addition to the mitotic count and primary tumour 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. Tumour 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 tumour 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 tumour response to imatinib treatment is of special concern.

treatment

Multidisciplinary treatment planning is needed (involving pathologists, radiologists, surgeons and medical oncologists), such as that which is available in reference centres for sarcomas and GIST, and/or within reference 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 tumours. 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 centre 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 tumour rupture is decreased). Following maximal tumour 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 tumour 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 in many presentations, depending on mitotic count, tumour size and site of disease. Given the efficacy of imatinib in the disease, adjuvant treatment with the drug has been studied. Overall survival data are still not available from any of the conducted studies, but one randomized, placebo-controlled trial demonstrated that imatinib dosed for 1 year in planned duration is able to prolong early relapse-free survival in completely resected >3 cm localized GIST. A longer follow-up is needed to draw definitive conclusions with regard to the absolute relapse rate after a substantial time interval, the length of the delay in relapse and the time to secondary resistance to imatinib in subsequently relapsing patients. Currently, there is no open trial of adjuvant imatinib. At the moment, there is no global consensus in the medical community on adjuvant imatinib as standard treatment for GIST patients with localized disease. Having been approved by regulatory bodies as EMEA and FDA, adjuvant imatinib can be proposed as an option for those patients with a substantial risk of relapse, for shared decision-making in conditions of uncertainty [II, C]. In addition to the risk assessment, mutational analysis may guide the selection of those patients who are more likely to benefit from the treatment. If the decision is made to use imatinib as an adjuvant, the currently available trial data support its use for one year. The results are awaited of a trial which compared one versus three years of treatment duration.

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 tumour 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 tumour 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 tumour 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 tumour 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. Data have been provided that a continuously dosed daily oral regimen with a lower daily dose may be effective and well tolerated, although no formal comparison has been performed within a randomized clinical trial. This schedule can therefore be considered 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 anecdotal 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 antityrosine 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

Antitumour activity translates into tumour shrinkage in the majority of patients, but some patients may show only changes in tumour density on CT scan, or these changes may precede a delayed tumour shrinkage. These changes in tumour radiological appearance should be considered as tumour response. In particular, even some increase in tumour size may be indicative of tumour response if tumour 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 tumour size and tumour density on CT scan, or consistent changes on MRI, should be considered as criteria for tumour response. FDG–PET scan has proved to be highly sensitive in early assessment of tumour 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 tumour progression after months of treatment equally amounts to tumour response. On the other hand, tumour progression may not be accompanied by changes in tumour size. In fact, some increase in tumour density within tumour lesions may be indicative of tumour 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, tumour size and tumour 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 tumours, 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.

note

These Clinical Recommendations update those formulated in 2008 following a consensus process based on a consensus event organized by ESMO in Lugano in October 2007. The consensus update in early 2009 and the previous event involved the same experts from the community of the European sarcoma research groups and from some sarcoma reference centres outside Europe. Their names are indicated hereafter. The text reflects an overall consensus among them, although each of them may not necessarily find it consistent with his/her own views. The EU-funded network of excellence CONTICANET (CONnective TIssue CAncers NETwork) supported the consensus process.

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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 expert authors and the ESMO faculty.

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