

Consensus meeting for the management of gastrointestinal stromal tumors

Report of the GIST Consensus Conference of 20–21 March 2004, under the auspices of ESMO

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Background: The management of gastrointestinal stromal tumors (GIST) has evolved very rapidly in the last 4 years. The objectives of this international consensus meeting were to describe the optimal management procedures for patients with GIST in localized and advanced stages, as well as research issues for the future.

Materials and methods: A panel of experts from six specialties, including pathology, molecular biology, imaging, surgery, medical oncology and methodologists for clinical practice guidelines from different European and extra European sarcoma societies were invited to a 2-day workshop. Several questions were selected by the organizing committee prior to the conference. Selected panelists reviewed the current levels of evidence for each point, and presented their conclusions during the meeting. These proposals were discussed, and consensus points were identified and categorized according to the Standard Options Recommendations (SOR) of the French Federation of Cancer Centers and National Comprehensive Cancer Network (NCCN).

Results: Thirty-two consensus points were identified, most from categories 2A of the NCCN and B2 of the SOR. Among these, the standard histological examination with immunohistochemical analysis using CD117, CD34, PS100, desmin and smooth muscle actin is considered standard. Molecular biology for the identification of *KIT* and *PDGFRA* mutation is an optional diagnostic procedure for GIST with negative CD117 staining, and otherwise is considered a research procedure. Complete tumor resection with negative tumor margins is the standard surgical treatment. Adjuvant imatinib after optimal tumor resection as well as neo-adjuvant imatinib remain experimental approaches to be performed within prospective clinical studies. Imatinib should be started at the date of diagnosis of metastatic relapse and given until development of intolerance or progressive disease. The optimal criteria for tumor response to imatinib remain to be delineated, and should include not only tumor size reduction or disease stabilization, but also reduction of tumor density (Hounsfield Units) on computed tomography and metabolic activity (i.e. reduction of FDG uptake on positron emission tomography). In a substantial proportion of patients, stable disease and even increase in tumor size may be associated with pathologic response to imatinib therapy, and available survival data indicate that the survival of these patients is similar to that of patients with conventional tumor response. Metastasis resection is an experimental procedure.

Conclusions: Consensus points in clinical management of GIST as well as questions for future clinical trials were identified during this consensus conference on GIST management.

Key words: consensus, ESMO, GIST, imatinib

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Introduction

Gastrointestinal stromal tumors (GIST) were described in 1983 as tumors in the gastrointestinal tract and mesentery, characterized by a specific histological and immunohistochemical

pattern. These tumors occurs at a median age of 60 years in most series, with a slight male predominance. Subsequently, GIST have been shown to exhibit typical activating mutations of the *KIT* or *PDGFRA* protooncogenes, which are the likely causal molecular events of GIST. GIST have a high risk of metastatic relapse, specifically in the liver and peritoneum, after initial surgery for localized disease [1–7]. Although GIST have been resistant to conventional chemotherapy in all retrospective and prospective studies reported so far [8–12], imatinib, a tyrosine kinase inhibitor blocking most mutated-activated *KIT* and *PDGFR α* proteins of GIST, controlled tumor growth in up to 85% of advanced GIST in the phase I, II and III trials reported to date [13–19]. The dramatic results achieved with imatinib for the treatment of advanced GIST have established imatinib as the paradigm of oncogene-targeted therapy in solid tumors.

Because GIST is a recently defined molecular and pathological entity, neither its management at initial diagnosis, nor the treatment of local and advanced disease has been standardized. Hence, clinical practice has been generally based on the analysis of retrospective series of patients and prospective series with limited follow-up, given that the first treatment with imatinib in a GIST patient was in 2000 [13]. The optimal management of localized GIST and advanced GIST in terms of histological diagnosis, surgery, imaging, medical treatment and molecular biology has been a very active scientific area over the last 3 years. There was therefore a need expressed by most experts in the field to exchange their current experience and knowledge, and to review the current state of the art in this rapidly moving field to try to delineate and discuss clinical practice guidelines for the management of these tumors. For this reason, the National Comprehensive Cancer Network (NCCN) established in 2003 an expansion and update of NCCN Clinical Practice Guidelines for the optimal management of patients with GIST [20]. To further extend these Clinical Practice Guidelines, a similar effort was promoted under the auspices of the European Society of Medical Oncology (ESMO). A multidisciplinary consensus meeting for the management of GIST involving 41 European, Asian, Australian and American expert physicians, pathologists, molecular biologist and surgeons was held in Lugano, Switzerland on 21–22 March 2004 under the auspices of ESMO. The goals were to identify a consensus as to the best practical approaches for treatment of GIST, to summarize these conclusions in a written document and to evaluate its impact on clinical practice. In addition to sharing experiences regarding clinical management of this disease, the meeting participants also discussed the NCCN guidelines recently developed in the USA for the treatment of GIST.

Materials and methods

Selection of participants

The meeting was initiated by ESMO members, who contacted selected physicians and researchers with a demonstrated expertise in the field of GIST and imatinib according to published literature, abstracts in major

oncology meetings, in particular ESMO, and participation in imatinib clinical trials. When a National Sarcoma Group was identified, the board was contacted to identify the potential participants at this consensus conference. Representatives from international and national sarcoma groups [EORTC Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, Scandinavian Sarcoma Group, Greek Sarcoma Group, Grupo Español de Investigaciones en Sarcomas, French Sarcoma Group, British Sarcoma Group, Swiss Sarcoma Group, Australasian Gastro-Intestinal Tumor Group, Japanese and German experts, and international societies (EORTC Soft Tissue and Bone Sarcoma Group)] involved in sarcoma management were therefore contacted and asked to select one representative from each of the following specialties: pathology, molecular biology, radiology, surgery, medical oncology, statistics and clinical trial methodology. In addition, representatives from the USA from each of the six subspecialties, as well as NCCN representatives, were invited to participate to the meeting. Overall, 41 investigators from 12 countries and all six fields of expertise participated in the conference (see Appendix 1).

Organization of the conference and methods

The conference was organized by ESMO with an unrestricted grant from Novartis Pharma and a private grant. Selected participants presented reports addressing specific questions raised by the organizing committee detailed in the Results section (e.g. what is the standard surgery for a localized GIST?), which were discussed in a general session by all panelists. The following questions were addressed and discussed: (1) histological diagnostic criteria for GIST; (2) molecular biology of localized GIST: a diagnostic or research procedure?; (3) standard imaging strategy for a localized tumor; what is optimal surgery for localized GIST?; (4) adjuvant treatment with imatinib: when? neo-adjuvant treatment with imatinib: when?; (5) standard imaging strategy for an advanced tumor: criteria of tumor response; (6) when should we initiate imatinib patient in GIST?; (7) imatinib treatment of advanced GIST: dose, duration; (8) surgery as first- and second-line treatment of advanced GIST: to whom?; (9) novel therapies: chemotherapy, targeted treatment, local destruction; (10) molecular biology of advanced GIST a routine or research procedure?; (11) new ways to analyze available and future data; (12) strategy for diffusion and prospective evaluation of the impact of these recommendations. The published available literature on GIST since 1983 was analyzed, as well as recent reports presented in international conferences.

Several topics on which a consensus could be reached were identified by the panel. Non-consensus points and questions for future trials were also identified. The present paper is the summary report of this meeting from the writing committee. A double validation procedure was undertaken: (i) the document was submitted for review to all panelists for approval (listed in Appendix 1: internal reviewers); and (ii) the document submitted to external reviewers (listed in Appendix 2: external reviewers).

Categories of consensus

The document summarizes the different conclusions proposed by the panelists with level of evidence according to the SOR (<http://www.fnclcc.fr/sor.htm>) and NCCN grading systems [20].

The SOR categories of consensus

The levels of evidence are depending on the type, quality and consistence of studies. Five levels are identified: level A: meta-analysis or consistent randomized clinical trial (RCT); level B: consistent RCT (B1) or prospective/retrospective studies (B2); level C: studies with questionable methodology of studies, or non-consistent results; level D: no data or case studies; expert agreement: no data, experts are unanimous.

The NCCN categories of consensus

Category 1: there is uniform NCCN consensus based on high-level evidence that the recommendation is appropriate; category 2A: there is uniform NCCN consensus based on lower level evidence that the recommendation is appropriate; category 2B: there is non-uniform NCCN consensus (but no major disagreement) based on lower level evidence including clinical experience that the recommendation is appropriate; category 3: there is major NCCN disagreement that the recommendation is appropriate. Of note, although the scale used by the present report were similar to that of NCCN GIST task force report [18], the conclusion proposed by the present panel may be different from this previous work.

Results of the Consensus meeting

The following issues were addressed during the meeting.

(1) What are the histological criteria for the diagnostic of GIST?

The panelists agreed that the diagnosis of GIST relies on standard histological examination, with a central review by an expert in sarcoma pathology for equivocal cases (SOR level B2, NCCN level 2A) [5]. The majority of cases can be classified into three broad categories: spindle cell type (70%), epithelioid type (20%) and mixed spindle and epithelioid cell type (10%). GIST of spindle cell type are composed of uniform eosinophilic spindle cells organized in short fascicles or in a short storiform growth pattern. The neoplastic cells tend to have light eosinophilic cytoplasm, often with indistinct cell borders. Nuclei tend to be oval-shaped and uniform in appearance, often with vesicular chromatin. Cystic stromal degeneration as well as stromal hemorrhage may represent a prominent feature. GIST of epithelioid type are composed of round-shaped cells exhibiting eosinophilic or clear cytoplasm. Nuclei tend to be round-to-ovoid and uniform, with vesicular chromatin. In comparison with spindle cell GIST, tumor cells tend more frequently to exhibit a nested growth pattern. GIST of mixed cell type may feature abrupt transition between spindle cell and epithelioid areas or, as an alternative, the two cell types may be intermingled. In approximately 10% to 20% of cases (of either spindle cell or epithelioid type), hyaline or fibrillary brightly eosinophilic structures known as skeinoid fibers can be seen [9]. These structures appear to be composed of nodular tangles of collagen fibers and typically exhibit PAS positivity. The relevance of these three histological subtypes to response to imatinib treatment, progression-free survival and overall survival remains to be investigated.

Immunohistochemical analysis of tumor samples using CD117 (positive in 95% of cases), CD34 (positive in 70% of cases), smooth muscle actin (positive in 40% of cases), PS100 (positive in 5% of cases) and desmin (positive in 2% of cases) is an useful adjunct for diagnosis (SOR level B2, NCCN level 2A) [7]. Approximately 5% of histologically suspected GIST are CD117 negative, and should be considered for molecular analysis for *KIT* or *PDGFR α* mutations. Immunohistochemistry should be performed without antigen retrieval since this may yield false-positive CD117 staining; similarly, Bouin fix-

ation should be avoided since it may impair the feasibility of molecular analysis on fixed samples (SOR level B2, NCCN level 2A).

For localized tumors, risk assessment profile based on the size and mitotic index per 50 high power fields according to a previous consensus report remains a standard procedure, although prospective evaluation of a large cohort remains to be performed [7, 21] (SOR level B2, NCCN level 2A). The prognostic value of grading is unclear in GIST. Other histological and molecular prognostic parameters, i.e. serosal breaching, may allow refining this classification in the future. Additionally, the importance of the primary site is still disputed; GIST from the small intestine may have a worse prognosis compared with gastric GIST (SOR level D, NCCN level 3).

(2) Is molecular biology for *KIT* and *PDGFR α* mutation a diagnostic or research procedure for GIST?

The panelists agreed that intra-abdominal tumors suspected to be a GIST in which CD117 immunostaining is negative should be considered for molecular analysis for *KIT* or *PDGFR α* mutations in expert laboratories (SOR expert agreement, NCCN level 2A). In other cases, this technique remains, in 2004, a research procedure, with possible clinical applications in the future. Clinical applications of these techniques will probably be routine in the future and specific expert laboratories should therefore be established in each country.

The optimal technique for mutation screening remains to be defined. *KIT* and *PDGFR α* mutation screening may be performed on either formalin-fixed paraffin-embedded or frozen tumor samples, provided that a routine histological examination of the sample has been performed before nucleic acid extraction. Tumor tissue microdissection may be useful to maximize the tumor cell proportion in the sample. So far, direct sequencing has been used in most of the studies to detect and identify *KIT* mutations; however, this technique may fail to spot somatic mutations when contaminating non-tumor cells are abundant. Length analysis of PCR products is more sensitive than direct sequencing for detection of deletions and insertions [22, 23], but does not detect point mutations. Denaturing high-performance liquid chromatography has recently been used to detect *KIT* and *PDGFR α* mutations in GIST [24–26], and is one of the most sensitive techniques for the detection of mutations [27].

(3) What is the recommended imaging strategy in localized GIST?

The panelists agreed that currently available imaging techniques to evaluate GIST include computed tomography (CT), magnetic resonance imaging (MRI) and fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET). Depending on local expertise and availability, contrast-enhanced MRI may be used in the initial evaluation of patients with GIST. Contrast-enhanced CT scan is, however, more widely available and is currently the imaging modality of choice for patients with suspected abdominal mass or

biopsy-proven GIST (SOR level B2, NCCN level 2A). At presentation, the primary GIST is often large, usually with an exophytic growth pattern (tumor grows between the bowel loops) and sometimes within the bowel lumen, although obstruction is rare, and heterogeneous when it becomes hemorrhagic, necrotic or degenerating. CT is used in staging and surgical planning. When a small tumor is found incidentally during endoscopy, the local extent of the tumor should be evaluated using either endoscopic ultrasound or CT. For those with known or suspected rectal GIST, a dedicated MRI provides better information than CT scan in preoperative staging work-up (SOR expert agreement, NCCN level 2A). Most metastases arise in the liver and peritoneal cavity, resulting from hematogenous spread (liver) and tumor peritoneal seeding for peritoneal metastasis. Metastasis can seldom be found in the pleura, lungs or soft tissues other than the abdominal wall, and lymph node metastasis are also rare. Evaluation of FDG uptake using PET scanning is recommended when an early detection of tumor response to imatinib treatment is required, e.g. for consideration of surgery after imatinib cytoreduction in rectal tumors (SOR expert opinion, NCCN level 2A). PET scan may also be useful in case of equivocal images suspected to be metastatic. Aside from these cases, PET scan is not mandatory in all GIST patients after complete resection (SOR expert agreement, NCCN level 2A).

(4) What is the standard surgery for localized GIST?

Biopsy

The panelists agreed that the standard treatment of localized resectable GIST is surgery. No consensus was achieved among experts regarding the need for a preoperative diagnosis by core-needle biopsies, taken either by endoscopic ultrasound or percutaneously (SOR level C, NCCN level 2B). If preoperative biopsy is scheduled, because these tumors are very fragile and may bleed easily, an experienced multidisciplinary team is preferred. Intra-abdominal open biopsy is discouraged by some of the experts because of the risk of tumorspill, unless multiple metastatic lesions are encountered.

Margins

Since GIST tend to grow out of, not diffusely infiltrate, the primary organ, wedge resection of the stomach or segmental resection of the intestine is considered an adequate treatment by the panel (SOR level B2, NCCN level 2A). For esophageal, duodenal and rectal primaries, however, wedge resections are often technically unfeasible, and therefore wide resections are the treatment of choice (SOR level B2, NCCN level 2A). In case of omental or mesenteric GIST, a complete *en bloc* resection of visible disease is recommended. Adjacent organs adherent to the mass should be resected *en bloc* with the tumor, in order to avoid capsule rupture and intra-abdominal spillage.

Although positive resection margins have not been definitely demonstrated to compromise survival, they may result in a higher risk of peritoneal relapse (i.e. metastatic disease)

[28–31]. The panel felt that a re-excision should be considered in case of intramural, intra-lesionally excised tumors, without infiltration of the serosal surface (SOR level C, NCCN level 2B).

Once the diagnosis of GIST has been established, the goal of surgery is complete resection of visible and microscopic disease, possibly avoiding the occurrence of tumor rupture and achieving negative margins [28–30]. Laparoscopic surgery should be avoided, owing to the higher risk of tumor rupture and subsequent peritoneal seeding (SOR expert agreement, NCCN level 2A). A laparoscopic resection might be accepted in cases of small (≤ 2 cm) intramural tumors. Margins should be negative within the organ from which the tumor originates, although the tumor may well involve the peritoneal serosal surface. Finally, the definitions of a localized resectable disease as opposed to an advanced non-metastatic disease were discussed during the meeting, with the conclusion that no reliable definition is possible given the diversity of size, site and extension of these lesions.

Lymphadenectomy

Unlike adenocarcinoma, GIST metastasize only rarely to local regional lymph nodes, and thus lymphadenectomy is warranted only for evident nodal involvement (SOR expert agreement, NCCN level 2A).

Resection versus watchful waiting

Since every GIST is now considered as potentially malignant [7], all GIST may need to be resected, even small intramural lesions of the gastrointestinal tract (SOR expert agreement, NCCN level 2B). However, since not all intramural lesions of the gastrointestinal tube are GIST, a preoperative pathological diagnosis should be obtained. Therefore, even in cases of small (≤ 2 cm) intramural tumors, shell-out procedures should be avoided, except in difficult locations (esophagus and rectum), provided the patient is informed and a careful follow-up is possible.

(5) Adjuvant treatment with imatinib: when?

This section focuses on adjuvant treatment with imatinib after macroscopically complete resection of a localized disease. Treatment with imatinib after complete resection of a metastatic disease is not considered as adjuvant by the majority of panelists and falls within the scope of drug registration in Europe and USA [32]. This aspect is discussed in section (8). In addition, GIST that are not amenable to macroscopically complete resection should be considered ‘unresectable’, and cytoreductive molecular-targeted therapy with imatinib mesylate, whether or not subsequent resection is feasible, falls within the scope of drug registration in Europe and USA [32].

Adjuvant imatinib should only be given in clinical trials

The panelists agreed that adjuvant therapy with imatinib mesylate remains investigational. Adjuvant imatinib might be able

to eradicate microscopic disease and lead to cure, but may also reduce the efficacy of the treatment of recurrent GIST and facilitate emergence of imatinib-resistant cell clones. Adjuvant imatinib treatment is the subject of ongoing clinical trials in those GIST patients who have a substantial risk of relapse after complete surgery. At present, two adjuvant trials are open in Europe. In the phase III trial conducted by the EORTC Soft Tissue and Bone Sarcoma Group as an intergroup study with the French Sarcoma Group, Italian Sarcoma Group, Spanish Group for Research into Sarcomas and Australasian Gastrointestinal Study Group, 400 GIST patients with either intermediate or high risk of disease recurrence are randomly allocated to receive 2 years of imatinib mesylate or no further therapy after complete surgery. The second trial is a randomised phase II trial conducted by the Scandinavian Sarcoma Group, in which 80 patients at high risk of disease recurrence or rendered free from metastatic disease by surgery, are randomized to either 12 or 36 months of adjuvant imatinib. In both studies the daily dose of imatinib is 400 mg. The American College of Surgeons Oncology Group ACOSOG-Z9001 study, currently running in the USA, will randomize 380 GIST patients with tumors ≥ 3 cm in diameter following complete surgery to receive either 400 mg imatinib for 1 year or placebo. The Radiation Therapy Oncology Group study RTOG-S0132 is assessing the use of neo-adjuvant and adjuvant imatinib. The results of these trials will not be available for several years, and, for the time being, adjuvant imatinib should thus be regarded as an experimental form of therapy. The use of adjuvant imatinib mesylate as standard therapy cannot be recommended in patients with localized GIST, and randomized trials with a no treatment control arm are considered ethically sound (SOR expert agreement, NCCN level 2A).

Candidate patients for adjuvant trials

Most clinical trials of adjuvant imatinib therefore include patients from the high or intermediate risk subgroups, according to the 2002 consensus risk classification [7], i.e. a patient group with a $>50\%$ risk of relapse [7, 21]. Among other risk factors, contaminated surgery may also result in a higher risk of peritoneal relapse (i.e. metastatic disease) [31]. Therefore, for research purposes, stratification amongst these patient categories should be encouraged. Although data on long-term follow-up of R1 patients is still needed, molecular-targeted therapy following macroscopically complete surgery with contaminated or with microscopically infiltrated margins should be labeled as 'adjuvant'.

Primary end point for adjuvant trials

The primary end point of these adjuvant trials was also discussed. It has not been demonstrated that molecular-targeted therapy in localized GIST is able to provide a chance of eradication of the tumor even in a high risk subgroup of patients. In addition, as mentioned below, RECIST criteria are not optimal for evaluating the benefits of imatinib in GIST patients. Therefore, progression-free survival rate may not be

the optimal end point for adjuvant trials, and it was felt that these trials should use overall survival as primary end point (SOR expert agreement, NCCN level 2A).

(6) Neo-adjuvant treatment with imatinib: when?

The panelists agreed that no data supported the use of neo-adjuvant imatinib when any decrease of tumor size will not affect surgery. This strategy is therefore not recommended outside of a clinical trial (SOR expert agreement, NCCN level 2A). Imatinib may be used, however, by multidisciplinary teams experienced in the management of GIST, imatinib treatment, surgery of digestive tract tumors and with the difficulties in the evaluation of imatinib response, in particular when function sparing surgery is the goal; this may be particularly frequent for rectal or esophageal tumors. However, some patients who have either unresectable GIST or GIST for which surgery would lead to a marked loss of organ function (e.g. a rectal GIST, when the anal sphincter cannot be preserved) may be treated with preoperative imatinib in an attempt to achieve cytoreduction and organ preservation. In these cases, a careful pretreatment and rapid treatment response assessment by PET and CT scan should be performed, with decisions being taken in a multidisciplinary discussion. Surgery may be performed after sufficient shrinkage (typically between 4 and 6 months). Because of the difficulties of evaluating tumor response and the risk of primary resistance, neo-adjuvant imatinib can not be considered as a routine procedure and should be provided only by a specialized team of physicians expert involved in sarcoma and GIST management (SOR expert agreement, NCCN level 2A).

These patients need to be distinguished from two different subgroups of patients: (i) those who have resectable GIST and who would receive preoperative ('neo-adjuvant') imatinib merely with the goal of eradicating suspected subclinical disease; this latter situation remains an experimental approach (SOR expert agreement, NCCN level 2A); and (ii) those in whom a metastatic disease (e.g. to the peritoneum) is surgically excised after a period of treatment with imatinib; this latter setting should be viewed as that of surgery of residual disease after molecular-targeted therapy for metastatic GIST. In particular, the prognosis of these patients is that of metastatic disease, and this situation falls within the conventional indications for imatinib, as registered in Europe and USA [32], whether a visible indicator of disease is present or not. In view of a recently reported randomized trial testing treatment interruption in advanced GIST patients, imatinib treatment must always be continued, even after complete resection of all visible disease.

The use of radiotherapy as neo-adjuvant or adjuvant treatment for GIST is not documented in the literature.

(7) How should patients be followed after resection of the primary tumor?

The panelists agreed that there are no reliable data in the published literature that could support specific recommendations

in this field; whether earlier treatment of advanced GIST with imatinib improves the outcome of these patients is unknown. Several proposals were made during the discussion. For high and intermediate risk, i.e. tumors >5 cm or with a mitotic index >5/50 high power fields [7], a reasonable follow-up would be a CT scan every 3–4 months for 3 years, then every 6 months until 5 years, and yearly thereafter. For low or very low risk tumors, i.e. tumors <5 cm and with a mitotic index <5/50 high power fields [7], systematic follow-up with CT scan every 6 months for 5 years was felt to be acceptable. At the present time, however, there is no evidence indicating that these are the optimal time intervals, and whether follow-up with CT is beneficial or not in these patients.

(8) When should imatinib treatment be initiated in patients with advanced GIST?

For unresectable and/or metastatic disease, the panelists agreed to recommend immediate treatment with imatinib (SOR level A, NCCN level 1). In case of equivocal images, or when the tumor(s) could be completely resected, such procedure may be discussed with the patient. Whether complete remission achieved by surgery may cure advanced GIST patient is unknown (see below) [29, 30].

Even when disease has spread to the peritoneal surface and/or to the liver, it may be completely resected in some patients. Available series in the pre-imatinib era show that complete resection, although technically feasible, is not curative in these cases. Therefore, imatinib mesylate is the therapy of choice after metastasis resection even in these presentations. The terminology ‘adjuvant therapy’ does not apply in the setting of metastatic spread of disease, whether resected or not. For clinical and research purposes, these presentations should definitely be separated from the properly ‘adjuvant’ framework, since their prognosis is that of metastatic disease. These patients fall within the conventional indications of imatinib mesylate for advanced GIST, as registered in Europe and USA [32], whether a visible indicator of disease is present or not.

(9) What is the optimal dose of imatinib treatment of advanced GIST?

The panelists agreed that 400 mg/day is the currently recommended dose in first-line treatment, since no overall survival improvement has yet been reported in the two large prospective randomized trials comparing first-line treatment with imatinib doses of 400 and 800 mg (SOR level B1, NCCN level 2A). Of note, however, both trials reported a superiority in terms of progression-free survival in the 800 mg arm, one reaching a significant statistical value (median progression-free survival 22 months versus not reached; $P=0.02$), the other being statistically non-significant (median progression-free survival 22 versus 27 months; $P=0.13$) [17, 18]. Longer follow-up is therefore needed; this conclusion may evolve in the future.

(10) How long should imatinib treatment be given in advanced GIST?

Imatinib interruption after 1 year is associated with a high risk of relapse, even for patients in complete remission, as shown in a recently reported randomized trial [19] and clinical experience. Although most (but not all patients) responded to imatinib reintroduction, the drug should not be discontinued outside of a clinical trial (SOR level A, NCCN level 1). Imatinib should therefore be given until progression, intolerance or patient refusal.

(11) Standard imaging strategy for an advanced tumor: criteria of tumor response

FDG PET has proven to be highly sensitive in detecting early tumor response [3]; however, it is costly and still limited in availability. CT is currently the imaging modality of choice in response evaluation (SOR level B2, NCCN level 2A), unless a very short-term follow-up of within 1–2 weeks is needed (e.g. to make a surgical decision for those with ‘marginally resectable’ tumors). The value of CT in very short-term follow-up has not yet been reported. MRI is also an option in particular for liver metastasis. The role of ultrasound is currently under investigation. Symptomatic improvement, CT scan [Hounsfield Units (HU) reduction], PET scan response are all predictors of tumor control by imatinib.

Tumor size, contrast enhancement, PET scan and response to imatinib

Although patients in partial remission according to RECIST clearly benefit from imatinib in terms of survival, imatinib is beneficial also in a substantial subset of patients with stable disease according to conventional tumor response criteria, and even in a subset of patients that undergo an initial increase in tumor volume. Once GIST respond to imatinib treatment, the mass becomes hypoattenuated on contrast-enhanced CT and the solid enhancing nodules and tumor vessels decrease (Figure 1) within 1 month in most GIST with ‘good response’ to therapy. Recognizing these patterns on CT in tumor response evaluation is important, since often, response in tumor size, particularly of the hepatic metastasis, is not apparent until late in therapy [35]. These patients generally show changes in tumor tissue characteristics on CT scan (i.e. reduction in tumor density measured by HU) or MRI, and/or changes in tumor metabolic activity at PET scan (decreased glucose uptake) (SOR level B2, NCCN level 1).

It should be noted that it is not uncommon for the tumors to become larger during the early post-treatment phase (within the first 6 months) despite significant clinical symptomatic improvement or FDG PET regression (Figure 1). Intratumoral hemorrhage, edema or development of myxoid degeneration may be responsible for this phenomenon. Use of tumor density measurement by CT attenuation coefficient (HU) can quantify early tumor response evaluation and may be helpful to distinguish this situation from genuine progression [36–38]. It has also been reported that tumor density on CT may predict

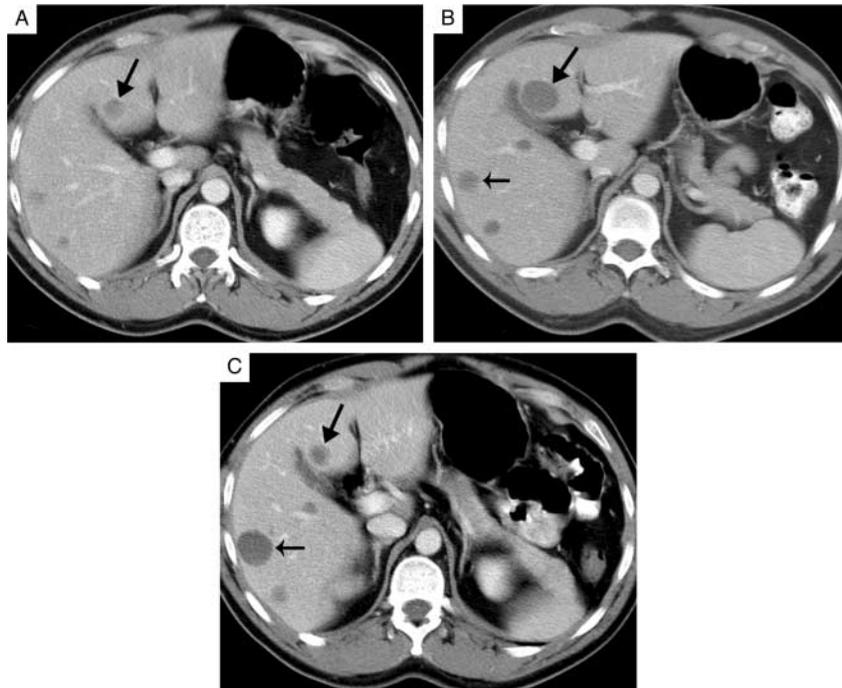


Figure 1. A 41-year-old male with primary of small bowel gastrointestinal stromal tumor with recurrent disease in the liver. (A) A portal-venous phase image of pretreatment computed tomography (CT) showed multiple small hyperattenuating metastases in the liver (arrows). (B) At 8 weeks after treatment, the lesions became homogenous and hypoattenuated but increased in size significantly (arrow). (C) At 16 weeks after treatment, the lesion in the medial segment of the left lobe decreased significantly. Notice the lesion in the right lobe (arrow) had continuously increased but remained hypodense. This lesion became smaller on the follow-up CTs (not shown). Lack of substantial change in tumor size during the early posttreatment period should not preclude a ‘response’.

the long-term survival as accurately as maximum standardized uptake value (SUV_{max}) on FDG PET [39]. Further investigation on the use of tumor density measurement is ongoing.

During the portal-venous phase images of enhanced CT, used routinely in general practice, the hypervascular hepatic metastases from GIST can become imperceptible because the enhancement of the tumors is similar to the enhancement of the surrounding hepatic parenchyma. These lesions can become hypodense on follow-up CT images when they are responding to treatment. These findings should not be misinterpreted as ‘new’ lesions or progression of disease. Well-performed triphasic imaging technique is necessary to recognize these hypervascular hepatic metastases. In most cases, however, unenhanced CT scan images may help to detect most of these lesions (Figure 2). Unenhanced CT images are also useful in detecting intratumoral hemorrhage. At the conclusion of this discussion, the panelists agreed that several parameters were predictors of tumor control by imatinib, including: (i) clinical symptomatic improvement under imatinib treatment; (ii) CT scan response and HU reduction; and (iii) a decrease of FDG uptake on PET scan (SOR level B2, NCCN level 2A).

Recurrences

Once the tumors have responded to therapy with a ‘good response’ or stabilization, the disease should be carefully monitored to detect recurrence. The consensus between experts was to propose a 3–4 month frequency for monitoring.

CT plays an important role in identifying recurrence. Recurrent disease in GIST treated with imatinib includes: (i) a new lesion at the site of surgical resection; (ii) a new metastasis; and (iii) increasing size of the pre-existing lesions. (iv) In addition, in a GIST patient receiving imatinib, development of an intratumoral nodule and/or an increase in ‘solid’ tissue, in the background of a hypodense lesion, is a unique finding of recurrence; this situation is not described within RECIST (Figure 3).

Each treated lesion should be carefully analyzed for any new intratumoral changes. Whenever a CT finding is inconsistent with the clinical picture or is inconclusive, FDG PET may be indicated for further evaluation, although the value of PET scan in a patient without a baseline study is limited.

(12) Surgical resection of residual metastasis in patients in whom advanced disease is controlled by imatinib?

The panelists agreed that no data currently indicate that surgery alone may cure advanced GIST. For patients who exhibit response or prolonged stable disease or for those who do not respond to imatinib, surgery is considered within several teams if all visible tumor can be removed; surgery takes place generally once the maximal response to imatinib has been reached. This usually happens between the fourth and 12th month after the onset of imatinib therapy. This procedure was considered by the panel to be still experimental; if considered, it should be performed by a multidisciplinary team experienced in

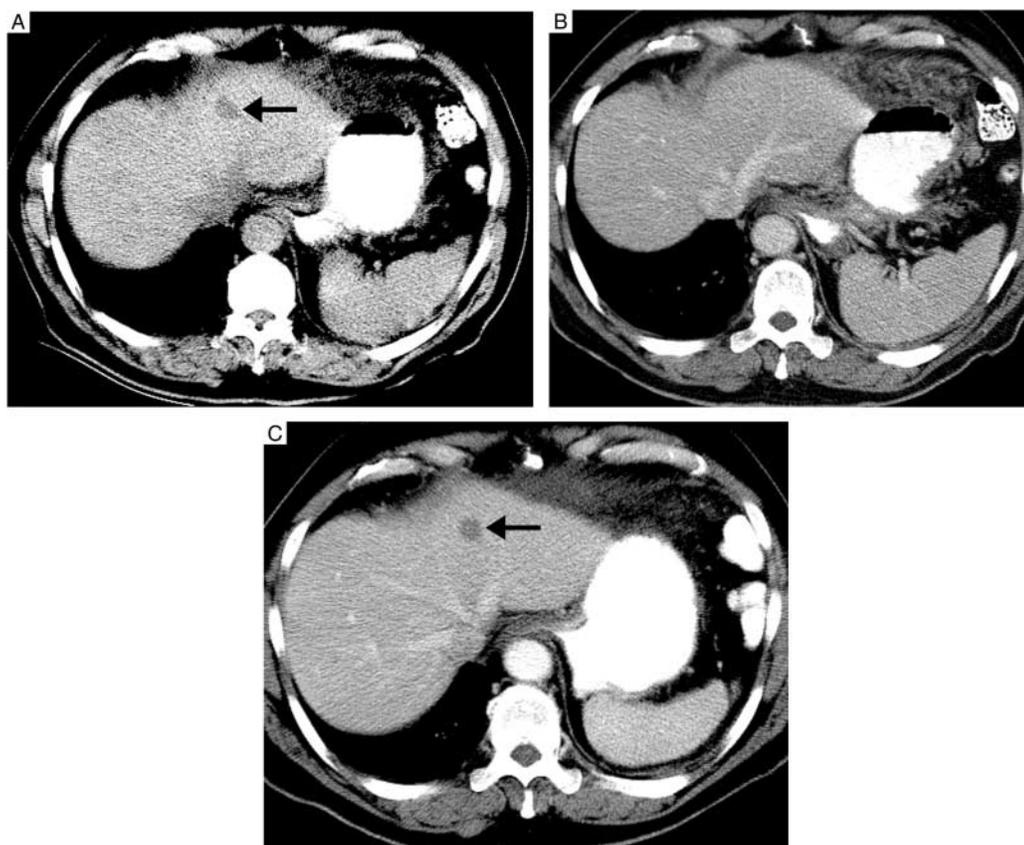


Figure 2. A 41-year-old male with primary gastrointestinal stromal tumor in the small bowel to the liver. (A and B) On pretreatment computed tomography (CT), the hyperattenuating metastasis (arrow) could only be detected on an unenhanced image (A), but not on the enhanced portal-venous phase image (B). (C) On a portal-venous phase image of CT obtained 8 weeks after treatment, the lesion (arrow) became clearly visible, mimicking a new lesion. Both unenhanced and enhanced CT images should be thoroughly analyzed.

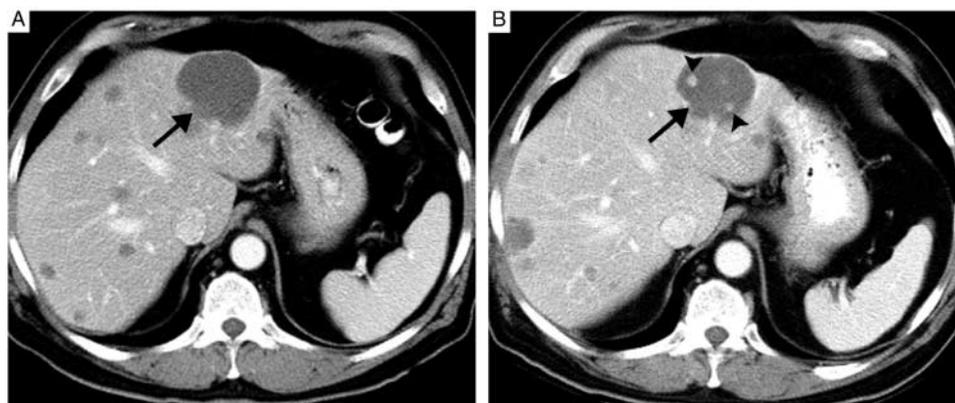


Figure 3. A 72-year-old male with primary gastrointestinal stromal tumor in the duodenum with recurrent disease in the liver. (A) An enhanced computed tomography (CT) image obtained at 12 months after treatment demonstrated multiple treated, hypoattenuating metastasis in both lobes of the liver. (B) On follow-up CT obtained at 22 months after treatment, new intratumoral nodules (arrows) had developed.

the management of these patients, and prospective patient registration and/or clinical trials needs to be implemented. Metastasis may be removed by resection, or experimental procedures such as destruction (e.g. radiofrequency ablation) (SOR level C, NCCN level 2B). Imatinib should not be interrupted, or interrupted for the shortest possible time because of the risk of tumor re-growth in this situation (SOR level A, NCCN level 1).

(13) What are the novel approaches after progression under imatinib therapy? Role of local destruction, targeted therapy and chemotherapy

It is noteworthy that several papers have reported a correlation between the nature of the molecular alterations of KIT and PDGFR α and response, as well as progression-free survival, under imatinib treatment [40–42]. This evaluation was

considered to remain a research procedure at the present time.

Panelists agreed that primary resistance and secondary resistance should be distinguished. Primary resistance is defined as progression within the first 6 months of imatinib therapy. This progression is generally multifocal. These tumors frequently exhibiting either wild-type KIT, mutations in exon 9 of KIT or a mutated PDGFR α with a D842V mutation. They represent therefore a distinct entity, although a still heterogeneous group of patients with regards to molecular biology.

Secondary resistance is therefore defined as resistance occurring beyond this first 6-month period. Secondary resistance occurs according to two different patterns, as follows.

(i) *Partial resistance.* One or a limited number of metastasis showing a nodule within a mass and/or enlargement with increased FDG uptake on PET scan, while the other sites remain controlled by imatinib treatment.

In this situation, a multidisciplinary approach is considered by some teams, including liver and/or peritoneal metastasis resections or radiofrequency ablation [29, 43, 44], along with an increased dosing of imatinib or an alternative experimental targeted therapy. However, the role of local treatment of metastatic disease in this setting has not been proven; a retrospective analysis of the results of these approach in these patients that have been most often included in a clinical trial would be useful to generate a hypothesis for a future clinical trial (SOR level D, NCCN category 2B).

(ii) *Multifocal resistance.* The role of radiofrequency ablation, tumor destruction or resection of liver and/or peritoneal metastasis or is even less well demonstrated. Again, increasing the dose of imatinib or an alternative experimental targeted therapy are options for patients in good clinical condition. This is a situation where no standard approach can be proposed.

In case of overt progression at the dose of 400 mg/day, an increase of the dose of imatinib to 800 mg/day yielded responses or prolonged tumor control in 34% of the patients in the EORTC-led intergroup 62005 trial, and 40% of the patients in the S0033 trial, with a median progression-free survival of 4 months for both trials, and a 12-month progression-free survival of 18% and 30%, respectively, for both trials [18, 45]. Increasing the dose of imatinib is therefore a recommended option in patients progressing on the dose of 400 mg/day (SOR level B2, NCCN level 2A). Alternative options include other tyrosine kinase inhibitors currently in clinical trials, such as the SU11248, which yielded a 7% response rate and 58% prolonged stable disease in a series of 92 imatinib-resistant GIST patients [58]. The panelists agreed that no chemotherapy agent had been demonstrated to be effective in this setting, and should be avoided outside of a clinical trial.

(14) Strategy for diffusion and prospective evaluation of the impact of this consensus meeting

The present consensus meeting was held in order to define the standard practice and guidelines to be recommended for the management of GIST patients as well as to identify unsolved

issues requiring prospective trials. Guidelines represent a collection of strategies that may be useful in managing a representative group of patients; they may serve to support clinical decision-making for the individual patient, and thus can improve the standard of care as well as the cost of health care [47–56]. If concordance with guidelines recommendations is measured at intervals, it is possible to detect changes in care patterns over time that may reflect quality improvement. After validation, the present consensus report may be disseminated to all practitioners involved in GIST patient care in order to provide information to specialists, physicians and patients, and to help the medical practice daily and possibly to make medical practices conform with evidence [57]. The anticipated dissemination strategy will include publication in *Annals of Oncology*, Internet dissemination and national implementation through national groups.

Impact of the guidelines on medical practices

The panel proposed a scheduled evaluation of the impact of these guidelines in different countries. The evaluation of the impact of these guidelines will identify conflicting issues (e.g. adjuvant treatment, initial staging or diagnosis of the disease). After the implementation phase, a survey and a clinical audit will be performed, with randomized physicians chosen as representatives of all medical subspecialists. The impact of the guidelines will be judged on the physicians' awareness of the existence of the consensus, knowledge of the conclusions and changes in medical management of patients observed in medical records.

Discussion

Since 2000, imatinib treatment for GIST has become the paradigm of oncogene treatment of solid tumors. As a consequence, the treatment of GIST has evolved rapidly, with dramatic changes in clinical practice. This GIST consensus meeting enabled us to identify consensus points for the management of GIST by European, Japanese and Australian specialists, in order to delineate guidelines for the general practitioner.

Thirty consensus points were identified on topics related to initial diagnosis, imaging, surgery, imatinib treatment and management of relapse. Most of these points were agreed upon by the majority of panelists. As expected, the clinical management of patients with advanced disease, in particular regarding evaluation of response, and any role of local destruction of metastasis, were the most difficult issues, since these treatments are palliative, and we do not yet know whether any of these patients will remain disease-free.

The aim of these guidelines is to improve the management of GIST patients. In addition, the dissemination and subsequent analysis of the impact of these guidelines in clinical practice will be useful to evaluate whether clinical practice guidelines improve medical practice in this rare tumor in which management is rapidly evolving. It has been shown that: (i) the elaboration of clinical practice guidelines may affect routine clinical practice, in particular for those

physicians involved in the making of these guidelines [59]; and (ii) that the outcome of sarcoma patients in whom guidelines were applied was significantly improved as compared with other patients [60]. A dissemination process that actively incorporates the clinicians in each country will therefore be useful to improve the management and care of GIST patients. Of note, the impact may be affected by the rapid evolution of this scientific field, which is likely to go on in the near future with the completion of adjuvant trials and the availability of second-line tyrosine kinase inhibitors. A regular update of these guidelines is planned.

This consensus meeting also enabled us to identify unresolved issues that may require a prospective analysis in the future. Among these, in addition to the ongoing adjuvant studies of imatinib in the localized disease setting: (i) the delineation of a simple algorithm to predict imatinib efficacy using probably composite parameters obtained from clinical, CT scan and PET scan evaluation would be useful; (ii) the role of surgery in advanced setting in consolidation treatment and treatment of partial progression should be better defined, as should the role of prolonged imatinib treatment in case of local progression. These issues will have to be addressed for future prospective trials.

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Appendix 1

List of participants

Name	Participation	Specialty	Country
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George Demetri	Organizer, chair	Medical Oncologist	USA
Pancras Hogendoorn	Presenter	Pathologist	The Netherlands
Raf Sciot	Presenter	Pathologist	Belgium
Haesun Choi	Presenter	Radiology/Imaging	USA
Sigrid Stroobants	Presenter	Radiology/Imaging	Belgium
Ninna Nupponen	Presenter	Molecular Biologist	Finland
Alessandro Gronchi	Presenter	Surgeon	Italy
Paolo Casali	Presenter	Medical Oncologist	Italy
Heikki Joensuu	Presenter	Medical Oncologist	Finland
Sylvie Bonvalot	Presenter	Surgeon	France
Axel Le Cesne	Presenter	Medical Oncologist	France
Ianis Boukovinas	Presenter	Medical Oncologist	Greece
Peter Reichart	Presenter	Medical Oncologist	Germany
Allan van Oosterom	Presenter	Medical Oncologist	Belgium
Jean-Francois Emile	Presenter	Pathologist/Molecular Biologist	France
Martine van Glabekke	Presenter	Statistician	Belgium
Isabelle Ray-Coquard	Presenter	Medical Oncologist	France
Maria Debiec-Rychter	Panelist	Molecular Biologist	Belgium
Pierre Meeus	Panelist	Surgeon	France
Jim Janinis	Panelist	Surgeon	Greece
Rosella Bertulli	Panelist	Medical Oncologist	Italy
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Andres Poveda	Panelist	Medical Oncologist	Spain
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Appendix 2

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Robert Maki	US SARC	Medical Oncologist	USA
Jaap Verweij	EORTC	Medical Oncologist	The Netherlands
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Karen Antman	NCI	Medical Oncologist	USA
Peter Hohenberger	EORTC	Surgical Oncology	Germany
Kirsten Sundby-Hall	SSG	Medical Oncologist	Norway
Piotr Rutkowski	EORTC	Medical Oncologist	Poland

EORTC, European Organization for Research and Treatment of Cancer; SOR FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer, FSG, French Sarcoma Group; US SARC, Sarcoma Alliance for Research through collaboration; SSG, Scandinavian Sarcoma Group; NCI, National Cancer Institute.