GASTROINTESTINAL STROMAL TUMOURS

PROGNOSTIC FACTORS IN LIMITED DISEASE

Staging procedures take into account the fact that most relapses affect the peritoneum and the liver. Contrast-enhanced abdominal CT scan is of choice for staging and follow-up. For rectal GIST, MRI provides better preoperative staging information. Chest CT scan or X-rays complements the staging workup of the asymptomatic patient. Standard treatment of localized GIST is complete surgical excision.

The risk of relapse can 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 did occur). Tumor size and mitotic count are considered in the 2002 Consensus Risk Classification. This has been correlated to 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 favorable prognosis. The “intermediate risk” category probably includes cases at low risk and cases with a higher likelihood of relapsing. 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 and rectal GIST. The risk estimate for subgroups is based on a single retrospective analysis, and therefore needs confirmation.

Retrospective data has pointed out that KIT deletions affecting codons 557 and 558 have independent prognostic value (Martin et al, JCO 2005). This prognostic proposal according mutations, should be confirmed in the prospective randomize trials (ACOSOG Z9000 and EORTC 62024) comparing IM therapy vs placebo in adjuvancy. The benefit of adjuvant treatment with imatinib has not been proved.

ADVANCED DISEASE

FIRST-LINE THERAPY

In locally advanced inoperable and metastatic patients, imatinib is standard treatment. This applies also to patients who have been completely relieved of the primary lesion and all metastases, being discovered unexpectedly at surgery. Not all patients with advanced disease had the same prognosis. Patients with poor perfomance status, high baseline neutrophil count and low albumin levels were significantly associated with worse overall survival (Blanke et al, JCO 2008, Verwej et al, Lancet 2004). Treatment should be continued indefinitely, since treatment interruption is generally followed by a relatively rapid tumor progression in virtually all cases, even when lesions have been surgically excised at some stage. Dose intensity should be maintained by proper management of side effects and a correct policy of dose reductions and interruptions in case of toxicity. Close monitoring of tumor response should be continued throughout treatment, since the risk of secondary progression does not decrease with time.

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 tumor shrinkage. These changes in tumor radiological appearance should be considered as tumor response to all effects. 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 only 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 proven 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.

Patients refractory to IM (early resistance) did not benefit to surgical rescue (12 months survival after surgery of 0%) (Raut et al, JCO 2006). The benefit of surgical rescue in metastatic GIST sensitive to IM has never been proved, and is currently analyzed in a randomized trial by EORTC and in a retrospective study by GEIS Group.

SECOND-LINE THERAPY

Despite of the initial activity, 80% of patients will progress during the first 5 years of therapy (Blanke et al, JCO, 2008). The standard approach in case of tumor progression is increasing imatinib dose to 800 mg daily.

Twenty per cent of patients treated with IM, present primary resistance and progress during the first 6 months of therapy and 12% are strictly IM refractory (progressive disease in the first 3 months of therapy) (Van Glabbeke et al, JCO 2005, Demetri et al, NEJM 2004). These patients usually presents a pattern of ‘’generalized disease progression’’ and are usually refractory to subsequent therapies. Biologically, they show kit exon 9 mutations, wild-type genotype or PDGF-R D842V mutations (Debiec-Rytcher et al, Eur J Cancer 2006).

Secondary resistance occurs in the rest of patients (60% of patients) and usually present ‘’limited disease progression’’ or the so called ‘’nodule in mass’’ suggesting that IM therapy still remains active at least in non-progressive lesions. Two major potential mechanisms of IM resistance are described: 1. KIT over-expression due to the acquisition of secondary mutations in KIT exons 13,14 and 17 or PDGF exon 18 (Chen et al, Cancer Res 2004; Antonescu et al, Clinical Cancer Res 2004; Wardelmann et al, Clinical Cancer Res 2006) which occurs in 50-70% of cases and 2. Activation of alternative RTK with c-KIT downregulation due to a kinase switch mechanism (Debiec-Rychter M et al, Gastroenterology 2004). In these patients a new alternative tyrosin-kinase receptor AXL, has been shown to be over-expressed (Mahadevan et al, Oncogene 2007), but the clinical impact has not been not fully clarified. Despite of the status of KIT, the PI3K-AKT remains the crucial survival pathway (Heinrich et al. JCO 2006; Bauer et al, Oncogene 2007). The fact that new KIT and PDGFR mutations appear at progression, will not probably rule that KIT-PDGFR independent pathways contribute also to acquired resistance.

Strategies in patients failing to imatinib

The prognosis of patients failing to IM is poor and less than 5-10% of patients respond to new therapies with alternative TK inhibitors. In addition, radiological evaluation is complex and there is no evidence that alternative methodologies to RECIST would be superior than RECIST itself. Despite of it, it’s seems clear that not all the lesions at IM progression by RECIST are without IM control. In fact the majority of lesions are still sensitive to IM. Therefore in randomized clinical trials evaluating new agents, using RECIST criteria, the control arm should be with IM therapy. New radiological methods for evaluating the activity of new drugs should be tested prospectively. Chemotherapy would be of value combined with imatinib or other TK inhibitors at IM failure. This strategy is being pursued in the GEIS Group.
Surgical and non-surgical procedures (such as ablations) may be an option in patients with limited progression, by RECIST criteria or the nodule in mass, in patients with acquired resistance. Nevertheless this local procedures used in limited progression has not shown proven benefit compared with second-line TK inhibitors.

REFERENCES

1.Martín J, Poveda A, Llombart-Bosch A, Ramos R, López-Guerrero JA, García del Muro J, Maurel J, Calabuig S, Gutierrez A, González de Sande JL, Martínez J, De Juan A, Laínez N, Losa F, Alija V, Escudero P, Casado A, García P, Blanco R, Buesa JM; Spanish Group for Sarcoma Research. Deletions affecting codons 557-558 of the c-KIT gene indicate a poor prognosis in patients with completely resected gastrointestinal stromal tumors: a study by the Spanish Group for Sarcoma Research (GEIS).J Clin Oncol. 2005 Sep 1;23(25):6190-8

2.Blanke CD, Rankin C, Demetri GD, Ryan CW, von Mehren M, Benjamin RS, Raymond AK, Bramwell VH, Baker LH, Maki RG, Tanaka M, Hecht JR, Heinrich MC, Fletcher CD, Crowley JJ, Borden EC. 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;26:626-32

3.Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, Issels R, van Oosterom A, Hogendoorn PC, Van Glabbeke M, Bertulli R, Judson I. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet. 2004;364:1127-34

4.Raut CP, Posner M, Desai J, Morgan JA, George S, Zahrieh D, Fletcher CD, Demetri GD, Bertagnolli MM. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors.J Clin Oncol. 2006;24:2325-31

5.Blanke CD, Demetri GD, von Mehren M, Heinrich MC, Eisenberg B, Fletcher JA, Corless CL, Fletcher CD, Roberts PJ, Heinz D, Wehre E, Nikolova Z, Joensuu H. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol. 2008;26:620-5.

6.Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002;347:472-80.

7.Van Glabbeke M, Verweij J, Casali PG, Le Cesne A, Hohenberger P, Ray-Coquard I, Schlemmer M, van Oosterom AT, Goldstein D, Sciot R, Hogendoorn PC, Brown M, Bertulli R, Judson IR. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australasian Gastrointestinal Trials Group study.J Clin Oncol. 2005;23:5795-804.

8.Debiec-Rychter M, Sciot R, Le Cesne A, Schlemmer M, Hohenberger P, van Oosterom AT, Blay JY, Leyvraz S, Stul M, Casali PG, Zalcberg J, Verweij J, Van Glabbeke M, Hagemeijer A, Judson I; EORTC Soft Tissue and Bone Sarcoma Group; The Italian Sarcoma Group; Australasian GastroIntestinal Trials Group. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours.Eur J Cancer. 2006;42:1093-103.

9.Chen LL, Trent JC, Wu EF, Fuller GN, Ramdas L, Zhang W, Raymond AK, Prieto VG, Oyedeji CO, Hunt KK, Pollock RE, Feig BW, Hayes KJ, Choi H, Macapinlac HA, Hittelman W, Velasco MA, Patel S, Burgess MA, Benjamin RS, Frazier ML. A missense mutation in KIT kinase domain 1 correlates with imatinib resistance in gastrointestinal stromal tumors. Cancer Res. 2004;64:5913-9

10.Antonescu CR, Besmer P, Guo T, Arkun K, Hom G, Koryotowski B, Leversha MA, Jeffrey PD, Desantis D, Singer S, Brennan MF, Maki RG, DeMatteo RP. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res. 2005;11:4182-90

11.Wardelmann E, Merkelbach-Bruse S, Pauls K, Thomas N, Schildhaus HU, Heinicke T, Speidel N, Pietsch T, Buettner R, Pink D, Reichardt P, Hohenberger P. Polyclonal evolution of multiple secondary KIT mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate.Clin Cancer Res. 2006;12:1743-9.
12.Debiec-Rychter M, Cools J, Dumez H, Sciot R, Stul M, Mentens N, Vranckx H, Wasag B, Prenen H, Roesel J, Hagemeijer A, Van Oosterom A, Marynen P. Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. Gastroenterology. 2005;128:270-9.
13.Heinrich MC, Corless CL, Blanke CD, Demetri GD, Joensuu H, Roberts PJ, Eisenberg BL, von Mehren M, Fletcher CD, Sandau K, McDougall K, Ou WB, Chen CJ, Fletcher JA. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol. 2006;24:4764-74.
14.Mahadevan D, Cooke L, Riley C, Swart R, Simons B, Della Croce K, Wisner L, Iorio M, Shakalya K, Garewal H, Nagle R, Bearss D. A novel tyrosine kinase switch is a mechanism of imatinib resistance in gastrointestinal stromal tumors. Oncogene. 2007;26:3909-19.
15.Bauer S, Duensing A, Demetri GD, Fletcher JA. KIT oncogenic signaling mechanisms in imatinib-resistant gastrointestinal stromal tumor: PI3-kinase/AKT is a crucial survival pathway. Oncogene. 2007 Jun 4;