2007 ASCO-REPORT
Gastro-Intestinal Stromal Tumour (GIST)

Sarcoma Patients EuroNet

Author (French): Axel Le Cesne, Gustave Roussy, Villejuif
Translation (English): Estelle Lecointe-Artzner
Review (English): Roger Wilson

ASCO 2017 was a very good event for soft tissue sarcomas and GISTs. A better biological/ cytogenetic understanding in general turns of each histological subtype identifying a potential target for new therapeutic approaches that will appear in the coming years. The intra-cellular signalling pathways are being unravelled in each histological subtype and molecular biology techniques are booming. Clinical trials are now based on molecular abnormalities (causative for some of them, secondary for others). Just this once, the most interesting communications dealt with biology and immunotherapy in sarcomas, with poster sessions as well as parallel sessions (like the one on GISTs) and the plenary have caught everyone's attention.

Seventeen years after the first patient treated with imatinib (Glivec®, Gleevec®, Novartis), the enthusiasm for GIST and the concept of targeted therapies in this disease seemed to revive this year with a parallel scientific session entirely dedicated to GISTs with some novelties. The teaching of ASCO 2017 on GIST can be summarized as following:

1. In adjuvant setting

Still no update neither of the US ACOSOG pioneer study comparing 1 year of imatinib versus placebo or nor of the EORTC study which was presented in 2013 (ASCO 2013, Casali et al, abstract 10500), comparing 2 years of imatinib versus simple surveillance. The German-Scandinavian study (SSG-AIO) presented six years ago in plenary (ASCO 2011, Joensuu et al, abstract LBA1) comparing 1 year of imatinib versus 3 years of imatinib in high risk GIST had been updated two years ago (ASCO 2015, H. Joensuu et al, abstract 10505). Recall that the German-Scandinavian study has modified the therapeutic standard. The superiority of the 3-year pattern remains steady in terms of 5-year RFS (P=0.003) and overall survival (P=0.032). The 5-year survival is 93.4% for patients who received 3 years of imatinib and 86.8% for those who received only one year.

The Persist-5 study was highly expected: this ongoing study is exploring the relevance of 5 years of imatinib in adjuvant setting (CP Rault et al, abstract 11009) in high risk GIST (all GIST > 2 cm and > 5/50 HPF, all non-gastric GIST > 5 cm). Ninety-one patients have been included in this non-comparative phase II study, the median duration of treatment is 55.7 months, nearly 50% of the patients could terminate the treatment, mainly due to patient's personal choice (42%) or to the side-effects (33%) classically observed with imatinib. Interestingly, pharmacokinetic analysis performed in some patients reveal: 1) the absence of a plasma level decrease over time (after 1 months and 1 year), unlike what was announced some years ago and 2) imatinib plasma levels are higher in females than in males, what could possibly explain why a majority of females classically become long responders in metastatic setting.

Only one relapse was observed during treatment and it was a patient with PDGFRa D842V mutation. Six other relapses were reported after treatment discontinuation. The patients who relapsed all had (except one) mutations for which: either imatinib was not indicated (2 Wild-Type GIST (WT) and 2 PDGFRa exon 18 mutated GIST including 1 with the D842V mutation), or the dose needed to be discussed (1 GIST exon 9)! Furthermore, a lot of these patients would have never been included in more recent studies (apart from the mutational status) according to their tumour size and mitotic index. If using the Joensuu classification (continuous variable of mitotic index and tumour size), about 1/3 of these patients presented an intermediate risk of relapse (even lower) for which the indication of adjuvant therapy was highly questionable. The 5 and 8 year PFS is respectively 90% and 81% and the 5-year overall survival is 95%.

These results can be favourably compared with the survival charts of the previous adjuvant studies even if these comparisons are historical. This study confirms what was already suspected: the extension of the adjuvant treatment duration postpone the delay of relapse in GIST harbouring imatinib sensitive mutations. But does it really prevent it? Some more time might be needed to judge and, with the absence of a control arm (3 years) it will difficult to come to any definitive conclusion.

2. In metastatic recurrence setting: first line therapy with imatinib

Patients who are long responders, still non-progressive under 400 mg of imatinib around their tenth year, or still alive under another therapeutic line have been analysed in two database of the French Sarcoma (Duffaud et al, abstract 11041): long responders/survivors (141 patients) benefited from a much more aggressive loco-regional approach than the others (in 29% of the cases during their first line therapy but also in 11% of the cases in 2nd and 3rd lines of TKIs). This concerns a large majority of GIST harbouring KIT exon 11 mutation (89% of the cases) but some WT GIST can also be found, as well as some exon 9 mutated GIST…And still under 400mg of imatinib! Discussions are still ongoing for a potential randomization of these long responders between treatment discontinuation and continuation (via EORTC)

3. GIST and mutations

Mutational status has become crucial in the management of GIST, in relapse setting but especially in adjuvant setting (ESMO guidelines 2014) as: 1) the benefit of imatinib on PFS relies on the mutational status 2) the frequency of insensitive mutations is high in localized GIST (PDGFRa D842V mutation observed in about 20% of the operated gastric GIST 3) the optimal duration of the administration of imatinib will tend to extend over time in high risk GISTs (PERSIST-5 trial, FSG ImadGIST ongoing study (3 years vs 6 years), the Scandinavian study (3 versus 5 years), 4) the number of available TKIs in advanced GIST increases over time, all with their own particularities (active or not on the novel mutations of the «ATP-binding pockets, KIT exon 13 and 14» area or of the «activation loop» KIT exon 17 and 18, 5) characterization becomes more and more complex in WT GISTs (some of

them now being called “quadruple negative” even “quintuple negative”: neither KIT, nor PDGFRa, nor NF1, nor BRAF, nor SDH).

Will it be possible to do without these new molecular biology tools? (NGS standing for New Generation Sequencing) in GIST? It was one of the topics presented during the GIST parallel session of very high scientific level (C.M. Kelly et al, abstract 11010). Yes and no. No because the cost of these approach is still prohibitive, because it remains in the field of fundamental research and because results still need to be correlated to clinical data. Yes because this technics allows to discover new horizons like: 1) the presence, in the primary tumour, of cellular clones already harbouring secondary mutations (which were thought as secondary to imatinib) like exon 17 mutations; 2) cellular pathways – rarely described - activated by KRAS or PI3K mutations in case of progression under imatinib but also of the CDKN2 pathway (56% of the cases), RB1, PTEN, JAK/STAT, MAPKinase, Hedgehog…; 3) In 177 evaluated patients, this NGS approach (410 analysed genes) allowed, according to the authors, the guidance of the therapeutic strategy in 79% of the cases with the same indication of an adapted therapeutic study in 12% of the cases. To be closely followed. Beside the genetic alterations, the nature of immune infiltrating cells of GIST which varies over time, with a majority of M2 type macrophages in metastatic and neo-adjuvant settings in poor histological responders (> 30% of residual tumour cells) and a majority of M1 type macrophages in good responders to imatinib administered in pre-operative setting (< 10% of residual tumour cells. The density of CD4 TILs and/or CD8 does not seem to be crucial for the identification of good and poor responders to imatinib (P. Hohenberger et al, abstract 11042)

A high level of PDGFD expression is an independent unfavourable prognostic factor in GIST (independently from Miettinen classification). In the case of STS, the expression of PDGFA is negatively correlated to patients’ survival (T. Lesluyes et al, abstract 11067)

4. Tyrosine Kinase Inhibitors (beyond first line therapy)

Apart from sunitinib (sutent®, Pfizer) and regorafenib (stivarga®, Bayer) which obtained a Market Authorization in 2006 and 2013 respectively in imatinib resistant/intolerant GIST, what will be the future of “ibs” in pre-treated GIST?

Sunitinib (sutent®, Pfizer): no communication this year.

Regorafenib (stivarga®, Bayer): no communication this year.

BLU-285 (Blueprint Medicines) is a small molecule selectively inhibiting - in pre-clinical models - KIT exon 17 mutations (almost present in every patient in 4th or 5th line of treatment) and PDGFRa D842V gene mutation. Furthermore, BLU-285 has 50% IC significantly lower than imatinib to obtain the same level of cell lines inhibition in practically all the mutations, including in WT lines. BLU-285 is superior to imatinib and regorafenib in terms of apoptosis, proliferative index and tumour decrease in Xenograft models. Sixty-one pre-treated patients (median number of previous lines is 4) have been included in the phase I-II testing of BLU-285 orally administered at doses starting from 30 to 600 mg/d

(MC Heinrich et al, abstract 11011). Results speak for themselves: 1) On the 25 current evaluable patients with GIST harbouring a PDGFRa exon 18 mutation (all D842V except 2 patients) 25 patients had a decrease of their tumour volume (100%) 15 (60%) have partial responses (according to RECIST) and the 10 others have stable disease (100% according to CHOI criteria). The only progressive patient under treatment had a GIST with a PDGFRa exon 14 mutation. The median PFS has not been reached yet; 2) On the 25 evaluable GIST patients with a secondary mutation (not determined yet), 8% have partial response according to RECIST criteria (50% if we only consider patients who received an optimal dose of BLU-285, > 300 mg), 32% have partial response according to CHOI criteria for a clinical benefit in 56% of the patients in total. The median PFS is 9.3 months given that patients are in their 4th therapeutic line or more (6 months in 2nd line with sunitinib, 5 months in 3rd line with regorafenib). The half-life of this molecule is 24 hours and the toxicities are similar to those observed with imatinib apart from nausea-vomiting which are more frequent with BLU-285. No doubt this molecule will become popular in a near future. A randomized study comparing BLU-285 to regorafenib is under preparation.

In such a context, how will crenolanib (AROG Pharmaceuticals) - which seems to be less effective in the initial studies – find its place (ASCO 2016, Von Mehren et al, abstract 11010) in GIST harbouring a PDGFRa D842V mutation? An international randomized (2:1) study comparing crenolanib to placebo is actually currently recruiting (JY Blay et al, abstract TPS11080). Note that crenolanib could also be active in GIST with KIT exon mutations involved in the mechanisms of resistance (not presented at ASCO).

imatinib/sunitinib re-challenge: when no therapeutic alternative is available for patients who experienced disease progression under the third lines of available and registered treatments (and no possibility to be included in any study), restart of imatinib or even sunitinib is a therapeutic option which can be considered and which is also recommended by the latest ESMO guidelines (2017, soon published): the re-challenge of imatinib in 74 Italian patients allowed a new control of the disease for a median duration of 5.4 months and prolonged survival (median 10.6 months), especially in patients with an initial KIT exon 11 mutation (B. Vincenzi et al, abstract 11038)

BGJ398 (infigratinib, Novartis)**,** FGFR inhibitor has been tested (according to two regimen of administration) in combination with 400mg of imatinib in 16 pre-treated patients (median of 4 lines of previous treatments). The MAP-kinase pathway (via FGF) can actually be involved in the mechanisms of resistance after failure to conventional treatments. On 12 evaluable patients, 9 had stable disease according to CHOI criteria with a median PFS of 8 weeks (C.M. Kelly et al, abstract 11039).