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Opinion

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Knowledge of the Molecular Signaling Pathways Improves the Chances of Treatment of Gastrointestinal Stromal Tumors

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INTRODUCTION

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal (non-epithelial) tumors of the gastrointestinal tract. A better molecular understanding of this entity, as Christopher L. Cordless in Modern Pathology in 2014[1] demonstrated, GISTs mainly a result from two-level changes in two Oncogenes: KIT oncogene (75%) and PDGFRA oncogene (α receptor platelet-derived growth factor) which occurs in about 10% of cases; the remaining 15% are designated wild type tumors.

Having knowledge of the oncogenic pathways of this condition, allows the possibility of creating models that stratify the risk of recurrence of GIST after surgery. This risk is determined by analyzing three factors (size, mitotic index and tumor location) in very low risk patients, low risk, medium and high risk, according to the model of "NIH" (National Institutes of Health). Patients with very low risk and low-risk tumors can perform only surgery; the intermediate risk and high risk may be indicated for adjuvant treatment. Emphasis on tumors where rupture of the tumor capsule occurs, always have indication for adjuvant treatment.

Imatinib is a tyrosine inhibitor developed in the early 1990's as a treatment chronic myelogenous leukemia due to its capacity of inhibiting the fusion oncoprotein BCR-ABL. Owing to structural similarities with KIT, several other experiments showed that imatinib can also inhibit the growth of cells that express mutant forms of KIT.[2] This demonstrated that imatinib has a strong activity against KIT – mutant GIST cell lines.

Until then, treatment options for patients with the diagnosis of GIST was poor. However, surgery was the state of art for localized GIST. With conventional chemotherapy the response rate was less than 5% with a median survival for advanced disease approximately of 18 months.[1] On the other hand, few data suggests that GISTS are sensitive to radiotherapy. It may have indication in a palliative situation, such as relief of symptoms, with a cumulative target dose of 30-50 Gy delivered in 2-3 Gy daily fractions.[3]

ADJUVANT TREATMENT

In 1998, S. Hirota, et al.[4] published an article in which the role of oncogene mutation kit and/or PDGFR in GIST was recognized. However, it was only in 2009 that imatinib was approved for the treatment of GIST expressing mutations in two oncogenes: KIT oncogene (exon 9 and exon 11) and oncogene PDGFR. This approval resulted from the American ACOSOG Z9001 trial[5] in which 713 patients were randomized into two arms (imatinib *vs.* placebo); in this study there was a statistically significant impact on recurrence-free survival in the imatinib group. (Table 1)

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But the European study AIO[6] randomized 400 patients with operable GIST with high risk of recurrence in two groups: one received imatinib for 12 months and the other imatinib for 36 months. The evaluation at five years showed that the results for the recurrence-free survival and overall survival were more favourable in the arm of patients treated for 36 months.

TREATMENT OF ADVANCED GIST

In cases where a patient was treated with imatinib and developed liver metastases, one of the recommendations may be increasing the dose according to the patient's tolerance and their comorbidities, since with this approach we may accomplish a good partial response and with a stable disease.[7] (Table 2)

Another approach was analyzed in the RIGHT Study[8] (Rechallange of Imatinib in GIST having no effective Treatment – phase III study design) where new patients treated with imatinib after a first approach with imatinib or sunitinib. The results showed a significant increase in progression free survival, but no improvement in overall survival.

Sunitinib is a second-line therapy that acts in mutations in where imatinib operates (KIT oncogene mutations in exons 9 and 11), also acting in mutations of exons 13 and 14 resistant to imatinib. The work Demitri GD, et al.[9] showed an improvement in progression free time of sunitinib (*versus* placebo).

For third-line treatments a new molecule appeared regorafenib, an oral tyrosine kinase inhibitor. Regorefenib is a multikinase inhibitor which acts against KIT, PDGFR and VEGFR. It inhibits the tumor micro-environment (PDGFR, FGRF),

		RFS (%) 1 year	HR 95% CI	OS (%)	HR 95% CI
ACOSOG[5] Z9001 n=713 median follow-up: 19.7 months	Imatinib 400 mg/ day	98	0,35, 95% CI 0.22-0.53 p<0.001	not reached	
	Placebo	83		not reached	
		RFS (%) 5 years	**HR** 95% CI	**OS (%)**	**HR** 95% CI
AIO[6] n=400	Imatinib 400 mg 12 months	48		82	
	Imatinib 400 mg 36 months	66	0.46, 0.32-0.65; p<0,0001	92	0.45 0.22-0.89 p=0.019

Table 1: Adjuvant Therapy.

		PFS months	HR 95%CI		
1st Line RIGHT Study[8] n=81 median follow-up: 5.2 months Placebo n=40	Imatinib 400mg n=41	1.8	1.7-3.6		
	0.9	0.9-1.7			
		TTP months	**HR 95% CI**		
2nd Line Demetri GD Study[9] n=312	Sunitinib 50mg/day 4w on+2w off n=207	6.3	0.33 0.23-0.47 p<0.001		
	Placebo n=105	1.5			
		PFS months	**HR 95% CI**	**OS**	**HR 95% CI**
3rd Line GRID Study[10] n=199	Regorafenib+ BSC n=133	4,8	0.27 0.18-0.39 p<0.0001	not reached	0.77 0.42-.41 p:0.199
	Placebo+BSC n=66	0,9		not reached	

Table 2: Paliative Therapy.

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proliferation of certain tumor cells (KIT, RET, RAF-1, BRAF, BRAF V600E) and also neoangiogenesis (VEGFR 1,2,3, TIE2). Regorafenib also inhibits GIST cells with primary exon 11 mutations and secondary KIT exon 17 imatinib resistant mutations, but is less active against KIT exon 13 (V654A) mutations compared with sunitinib.

The study that led to the approval of this molecule, GRID[10] (Regorafenib in Progressive Disease – phase III study design), where 199 previously treated patients with metastatic GIST unresectable were randomized into two groups: one group of patients was treated with regorafenib and best supportive care, another group was treated with placebo and best supportive care. The median progression-free survival was 4.8 months *vs.* 0.9 months, with clear superiority on regorafenib arm. This arm also presented a reduction of 73% in the risk of progression or death.

FUTURE

Based on pharmaco-economic studies recently published in Oncologist,[11,12,13] it should be emphasized that despite the adjuvant treatment with imatinib has a significant economic impact on the national health system, its' use allows a better approach in relation to cost-benefit level, regarding each patient. Nevertheless, the recurrence of GISTs is also associated with an economic and social cost, that are not negligible.

The optimization of targeting multiple pathways, in the treatment of GISTs will, provide a therapeutic approach aimed at the molecular tumor profile, with greater benefit for the patient and the doctor with a better global outcome.

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