World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i16.2583

World J Gastroenterol 2013 April 28; 19(16): 2583-2586
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Role of molecular analysis in the adjuvant treatment of gastrointestinal stromal tumours: It is time to define it

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Received: February 6, 2013 Revised: March 25, 2013
Accepted: April 3, 2013
Published online: April 28, 2013

Abstract

Sendur *et al* pointed out the attention on the importance of mutational analysis for adjuvant treatment of gastrointestinal stromal tumor (GIST) in an article published in *World Journal of Gastroenterology*. In particular, they suggested that the optimal dose and duration of adjuvant therapy could be defined by the mutational status of the primary disease. This comment would underline the importance of centralised laboratories, given the increasingly important role of molecular analysis in the work-flow of all GIST, and the need of retrospective analyses for subgroups population stratified for the mutational status from the available studies in the adjuvant setting, in order to define the role of mutational analysis in choosing the optimal dose and duration of adjuvant therapy.

Key words: Gastrointestinal stromal tumours; Platelet-derived growth factor receptor alpha; KIT; Wild-type; Molecular analysis; Imatinib; Adjuvant treatment

Core tip: Sendur *et al* pointed out the attention on the importance of mutational analysis for adjuvant treatment of gastrointestinal stromal tumor (GIST). In particular, they suggested that the optimal dose and duration of adjuvant therapy could be defined by the mutational status of the primary disease. This topic represents a big challenge in GIST's management by now, because even if the molecular analysis is strictly recommended in the work-flow of all GIST, its role in the adjuvant setting remains still unsettled due to the lack of prospective large clinical trials. In particular we pointed out the attention on the KIT/platelet-derived growth factor receptor alpha wild type GIST, that are extremely heterogeneous both in clinical and molecular background, making difficult their management also in the adjuvant setting. Our comment would underline the importance of centralised laboratories, given the increasingly important role of molecular analysis in the work-flow of all GIST, and the need of retrospective analyses for subgroups population stratified for the mutational status from the available studies in the adjuvant setting, in order to define the role of mutational analysis in choosing the optimal dose and duration of adjuvant therapy.

Nannini M, Pantaleo MA, Biasco G. Role of molecular analysis in the adjuvant treatment of gastrointestinal stromal tumours: It is time to define it. *World J Gastroenterol* 2013; 19(16): 2583-2586 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i16/2583.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i16.2583

TO THE EDITOR

We read with great interest the article by Sendur *et al*[1] entitled "Is exon mutation analysis needed for adjuvant treatment of gastrointestinal stromal tumor?", that has been recently published in the January issue (2013) of *World Journal of Gastroenterology*. The authors pointed out the likely importance of mutational analysis for guiding

the clinicians in the treatment's choice of gastrointestinal stromal tumor (GIST) patients also in the adjuvant setting[1]. In particular they suggest that the optimal dose and duration of adjuvant treatment could be defined by the mutational status of the primary disease. Their account comes from the consolidated evidence that the mutation status is predictive of response to imatinib treatment in the advanced disease[2-5]. In fact it is well known that *KIT* exon 11 mutations are associated to the highest response rate to imatinib in comparison to patients exon 9 mutations[2,3]. On the contrary exon 18 *PDGRFA* D842V point mutation confers primary resistance to imatinib[4,5]. Furthermore it has been widely shown that the subgroup of patients with *KIT* exon 9 mutation treated with imatinib 800 mg had an higher progression-free survival in comparison with those treated with the standard dose of 400 mg[6]. Translating these evidences from the advanced disease to the limited disease the authors suggested that it may be reasonable to assume that patients with a substantial risk of GIST relapse harbouring *KIT* exon 9 mutation should be considered for higher dose of adjuvant imatinib.

Moreover, in the last years the potential role of mutational status as a prognostic factor has been progressively appeared[7]. In particular, it has been shown that deletions of *KIT* exon 11, especially those involving codon 557 and/or codon 558 are associated with a shorter progression-free and overall survival whereas most platelet-derived growth factor receptor alpha (*PDGFRA*)-mutant GISTs generally have a lower potential for malignancy[8-15].

By now even if the optimal duration of adjuvant imatinib therapy is still unclear, adjuvant imatinib for three years of duration as a standard of care in high-risk operable GISTs is recommended[16,17].

Whether the role of mutational status as a prognostic factor should be confirmed in large series, the authors suggest that the optimal duration of adjuvant treatment could be different in relation to the kind of mutation found and not only to the standard prognostic factors.

Based on the above considerations, the mutational analysis is strictly recommended in the work-flow of all cases of primary GIST, because it provides information about tumour sensitivity to imatinib and, although not yet included in any risk stratification system, it may provide prognostic information[17-19]. However, the decision-making on adjuvant therapy treatment based on mutational analysis alone is not still supported by consistent data, with the exception of *PDGFRA* D842V mutation[17].

In particular, the adjuvant therapy in the *KIT*/*PDGFRA* wild type (WT) GIST, which notably may be less sensitive to imatinib than most mutated GIST, remains controversial. In fact, in recent years is emerging more and more the idea that *KIT*/*PDGFRA* WT GIST should be considered as a heterogeneous group of disorders rather than a single molecular subtype of GIST, both in clinical behaviour and molecular background[20-27]. For example, it has been recently identified a subgroup of *KIT*/*PDGFRA* WT GIST, characterized by germline and somatic mutations in succinate dehydrogenase (*SDH*) subunits B, C and A and defined in different ways as *SDH*-decifient GIST, or type-2 or pediatric-type GIST[24-27]. These patients have in common several pathological and clinical features, such as the epitheliod pattern, the multifocal presentation, the female prevalence, the gastric primary tumor localization, and the indolent course of disease despite the presence of lymph nodes and liver metastases up-front and independently to standard prognostic parameters. Moreover it seems that they have also a questionable sensitivity to imatinib. Given their indolent behaviour when metastatic, *KIT*/*PDGFRA* WT GIST *SDH*-deficient may not benefit from adjuvant treatment irrespective to the standard risk stratification, whereas more aggressive *KIT*/*PDGFRA* WT GIST without *SDH*-impairment, may be probably considered as all mutated GIST.

Therefore also the effect of adjuvant imatinib on *KIT*/*PDGFRA* WT GIST may be variable and clinical decision-making should be individualised case by case taking into account various molecular data and shared with the patient[17].

In conclusion, given the increasingly important role of molecular analysis in the work-flow of all GIST, centralised laboratories should be widely warranted. Furthermore, the special attention pointed up by the authors on the "optimal dose" and the "duration" of adjuvant treatment defined by the mutational status of the primary disease should be used at first for the decision to suggest or not the imatinib treatment in this setting. Finally, since prospective clinical trials with large series for definitely defining the role of mutational analysis for patients stratification, dose selection and treatment duration in the adjuvant setting, are difficult because the rarity of disease, retrospective analyses for subgroups population stratified for the mutational status from the available studies in the adjuvant setting are necessary.

ACKNOWLEDGMENTS

Members of GIST Study Group, University of Bologna, Bologna, Italy: Annalisa Altimari, Annalisa Astolfi, Paolo Castellucci, Rita Casadio, Fausto Catena, Claudio Ceccarelli, Valerio Di Scioscio, Giorgio Ercolani, Stefano Fanti, Michelangelo Fiorentino, Serena Formica, Pietro Fusaroli, Valentina Indio, Lidia Gatto, Walter Franco Grigioni, Elisa Gruppioni, Cristian Lolli, Alessandra Maleddu, Anna Mandrioli, Pier-Luigi Martelli, Maria Caterina Pallotti, Paola Paterini, Maria Giulia Pirini, Antonio Daniele Pinna, Donatella Santini, Maristella Saponara, Milena Urbini, Maurizio Zompatori.

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