‘All action no talk’: the role of HER2/neu in adjuvant therapy choice for gastric cancer

HER2 protein is a transmembrane tyrosine kinase receptor belonging to the HER family. HER2 is known to be involved in the pathogenesis of several human cancers and its overexpression and/or amplification, in the last three decades, has been robustly associated with poor prognosis in breast cancer, leading to the use of trastuzumab and other anti-HER2 targeted agents as the backbone of HER2-positive patients’ treatment [1].

The interest in studying the role of HER2 in gastric cancers has developed differently. The pivotal work [2] demonstrating the prognostic value of the HER2 gene in gastric cancer was published at the beginning of 1990s, but for the following 20 years, a large variation in the rate of HER2 positivity (ranging from 44 to 53.4%) across different studies [3] was found.

This lack of consistency can be partly attributed to the differences in study populations, but especially to the use of non-standardized methodology (mainly based on IHC) and different scoring criteria. Things changed when the majority of researchers adopted the scoring criteria developed by Hofmann et al. for the ToGA trial [4], which reduced the variation to a range of 9.4%–15.7% [5–9]. However, it is not surprising that the potential prognostic role of HER2 in gastric cancer is still under debate [10, 11]. Although most of the authors have found significant correlation between HER2-positive status and poor outcomes, others have not demonstrated any association between HER2 expression and prognosis [3]. The results from the ToGA [5] trial further complicated this issue as the study showed a longer than expected (historical controls) overall survival of patients who received chemotherapy alone, leading the authors to take into account a possible role of HER2 overexpression in conferring a better prognosis. Therefore, the authors concluded that further studies were needed to obtain a definitive answer about the prognostic role of HER2 in gastric cancer. Although trastuzumab is, so far, the only targeted therapy that has demonstrated in a randomized trial a modest but clinically significant improvement in survival when combined with chemotherapy as first-line treatment in metastatic gastric cancer, further research aiming to elucidate the actual biological and prognostic role of HER2 overexpression in this disease would seem to be mandatory.

The contribution provided by Gordon et al. [12] interestingly describes the role of HER2 status in an unexplored landscape of the chemo-radiation adjuvant setting. In particular, the authors investigated the potential prognostic and/or predictive role of HER2 amplification/overexpression using the population of the SWOG9008/INT-0116 trial. In this phase III trial 582 patients with resected stage IB-IV (M0) gastric and gastroesophageal (GE) junction cancer were randomly assigned to postoperative adjuvant therapy with 5-fluorouracil (5-FU)/leucovorin plus external beam radiation versus observation. After a median follow-up of 10 years, a survival advantage was observed in all subsets of patients treated with postoperative chemoradiation (except for cases with diffuse histology) and HER2 positivity status was able to independently predict a lack of benefit from adjuvant chemo-radiation, especially considering that none of the 28 HER2-positive cancers had diffuse histology [13]. These data are in accordance with previously reported preclinical evidence suggesting a possible role of HER2-mediated PI3K/AKT pathway activation in reducing cytotoxicity of 5-FU and radiation in breast cell lines [14–17] and with the reported reduction in resistance of HER2 overexpressing gastric cancer cell lines treated with trastuzumab [18]. Therefore, this study could represent a step forward in understanding the clinical utility of HER2 assessment in gastric cancer patients as it elucidates for the first time in the literature a predictive role in the adjuvant setting in a phase III prospective trial. Furthermore, despite not being able to reach a conclusion regarding the prognostic role of HER2 status in the postoperative setting, given the low number of HER2-positive cases, these results support the rationale to further consider this biological marker as one of the possible parameters to guide clinical decisions regarding adjuvant treatment. To note, despite the paper by Gordon et al. having a robust methodology, some factors should be taken into consideration in order to better understand the global value of this analysis. The first concern is related to the molecular analysis which was done retrospectively and was not planned in this clinical trial: <50% (258 of 559) of the enrolled patients had pathological specimens available and this could reflect a selection bias. Second, the balance of the main clinical and pathological characteristics between the two arms has not been analysed in the HER2/neu-positive patients. Third, the number of HER2-amplified cases is lower than the findings in previous reports [10]. This result is particularly relevant if we take into account that GE junction cancers. It is well documented that GE junction cancers show a higher rate of HER2 amplification, in contradistinction to the results reported by Gordon et al. Finally, it is also worth pointing out that the level of concordance between in situ hybridization methods (FISH and SISH) and IHC positivity seems to be considerably lower compared with the ones in ‘post ToGa era’ studies. One explanation for this weak correlation could be related to the IHC scoring criteria used for the study. As mentioned by the authors, the common breast cancer scoring system (BCSS) [19] has been applied to carry out the work instead of using the...
specific gastric cancer scoring system (GCSS) developed by Hofmann et al. [20] used in the ToGa trial. Although very similar, the two systems differ in one key point as, in GCSS an incomplete basolateral membrane staining is accepted while in BCSS is considered negative. Recently it has been demonstrated [21] that applying GCSS provides both a higher degree of concordance with in situ hybridization methods and a clear gain in sensitivity compared with the use of classical BCSS. Furthermore, it is not clear what is stated in the methodology section, whether the IHC staining was carried out on postoperative histological sections or on previously collected diagnostic endoscopic biopsies. This information could be particularly relevant as in the latter scenario, it would have been impossible to carry out any normalization procedures to account for the non-neoplastic peritumoral epithelium. Indeed in an interesting work on breast cancer, Gown et al. [22] clearly demonstrated a gain of 30% in concordance with FISH using a normalized HER2 IHC score that subtracts the score on the benign cells from that on the tumour cells.

In conclusion, what is the impact of the study conducted by Gordon et al.? It provides for the first time in the literature a potentially useful algorithm to help us selecting the best adjuvant choice in radically resected gastric cancer patients. Until now, we did not have any clinical, pathological or molecular predictive factors suggesting a potential benefit from adjuvant chemoradiation after radical surgery in gastric cancer. If there is a real weakness in the present study, it derives from the low number of HER2 FISH-positive patients included in the analysis. This limitation did not permit the authors to investigate the real prognostic role of HER2 amplification in gastric cancer without macroscopic residual disease. However, we cannot completely translate the role of HER2 in predicting benefit from adjuvant chemoradiation in the EU clinical scenario, where the best practice in the adjuvant gastric cancer setting is 5-FU-based chemotherapy without radiotherapy.

This paper is interesting and innovative, but external validation in prospective adjuvant trials aimed at validating the role of HER2/neu amplification as a predictive factor for resistance in the adjuvant setting is warranted, before this approach becomes the state-of-art.

What can we expect in the next decade? HER2/neu testing will be probably become mandatory also in the adjuvant setting when we will have the availability of the new and highly effective targeted molecules developed for breast cancer, such as lapatinib, pertuzumab, TDM1 in gastric cancer. Finally, in the near future we hope to increase the accuracy of HER2/neu determination in gastric cancer (currently imperfect) with the aim of selecting the right bullet for the known target and reduce the risk of treating false-positive patients or not treating false-negative ones.

D. Santini1*, B. Vincenzi1, F. Pantano1,3, G. Schiavon2 & G. Tonini1

1Medical Oncology Department, University Campus Bio-Medico, Rome, Italy
2Breast Unit, The Royal Marsden NHS Foundation Trust, London, UK
3INSERM, Research Unit U1033, University of Lyon-1, Faculty of Medicine Laennec, Lyon, France (*E-mail: d.santini@unicanpuss.it)

Disclosure

The authors have declared no conflicts of interest.

References

5. Im SA, Kim JW, Kim JS et al. Clinicopathologic characteristics of patients with stage II/IV (M0) advanced gastric cancer, according to HER2 status assessed by immunohistochemistry and fluorescence in situ hybridization. Diagn Mol Pathol 2011; 20: 94–100.
Annals of Oncology


Therapeutic windows and opportunity cost cast upon prostate cancer’s fatal shore

The last 3 years have seen a myriad of new therapies for advanced castration-resistant prostate cancer (CRPC), including immunotherapy, novel chemotherapy, two hormonal agents and bone calcium matrix targeted radionuclide. For patients and clinicians involved in making decisions on treatment in these settings, each therapy is welcome but presents a challenge of which patient it is best used in, when and in what sequence. Generally, new cancer agents are developed in an artificial vacuum, where the new treatment is considered in a phase III construct that is defined ahead of time with an agreed end point to facilitate regulatory approval funding. This paradigm fundamentally ignores the fact that standard therapy may change over the course of a clinical trial and alter assumptions made in designing the trial. In the setting of CRPC, this was not a challenge, because only docetaxel (Taxotere) demonstrated a required overall survival advantage, and newer agents were orientated relative to it: ‘pre’ or ‘post’ docetaxel. Most agents were moved into phase III trials after docetaxel because it was considered a lower risk; a trial run before docetaxel might have a poorer chance of demonstrating an overall survival benefit because sequent treatment with chemotherapy would dilute any difference between the study arms.

In the context of the development of two new classes of hormonal agents directed at the androgen receptor signaling pathway in prostate cancer, androgen biosynthesis hydrolase inhibitors and second-generation androgen receptor antagonists, the prototypical drugs were each tested in phase III trials before and after chemotherapy with a requirement that patients had not received the other novel agent. The post docetaxel trials, the Cougar 301 trial for the androgen biosynthesis hydrolase inhibitor, abiraterone acetate, and AFFIRM trial for the second generation androgen receptor antagonist, enzalutamide, accrued first and were followed by pre-docetaxel trials called Cougar 302 and PREVAIL respectively [1–3]. The question about optimal sequence of each of these drugs relative to the other has been of considerable interest but is currently dictated by regulatory approval of abiraterone acetate in the pre and post docetaxel setting and enzalutamide only in the post-docetaxel. On that basis, if patients are to receive both agents then they are likely to get abiraterone first and then possibly docetaxel followed by enzalutamide. This issue of whether one mechanism of inhibiting the androgen receptor axis followed by the other may be additive, neutral or negative for the second agent has not been addressed, until now.

Two articles in this edition of Annals report on the efficacy and safety of abiraterone in patients previously treated for metastatic CRPC. The key endpoints of these study cohorts and the abiraterone treated patients from the Cougar 301 study are summarized in Table 1. Loriot and et al. report a shorter duration of effect and less serum PSA kinetic change in 38 patients given abiraterone and prednisona after docetaxel and enzalutamide [4]. The enzalutamide was given as part of the AFFIRM trial [3] and patients who were randomly assigned to placebo in that trial and treated with abiraterone with no prior enzalutamide had longer and better responses to abiraterone than those that received enzalutamide on the trial. In the North American study, patients previously treated with enzalutamide had short median PFS and less robust PSA responses than experienced by patients given abiraterone after prior docetaxel in the Cougar 301 trial [1, 5]. Patients in this cohort at the commencement of abiraterone were more likely to be on opioid analgesia and had higher serum alkaline phosphatase and lactate dehydrogenase levels than when they commenced enzalutamide therapy. These factors are indicative of increased disease burden and morbidity when the patients commenced the second agent. Neither the duration of response nor the depth of PSA response to prior enzalutamide correlated with subsequent response to abiraterone. There were recorded responses to abiraterone in patients with early resistance to enzalutamide. There is no suggestion of excess toxicity or safety concerns from abiraterone in these groups of enzalutamide-treated patients. It is not possible for us to construct a definitive comparison of enzalutamide exposed and non-exposed patients with the data from these cohorts. In addition, the rigor of patient selection does not come close to that of a formal clinical trial and the endpoints, which are largely PSA based, would be considered only surrogate markers of potential benefit in our clinical trials. Despite this, these are the best data we have and bear analysis simply because they may help inform clinical decisions in the absence of level 1 evidence. The duration of response and proportion falling to a PSA <50% of baseline are very similar for patients given abiraterone after the placebo arm of AFFIRM and abiraterone given in Cougar 301, while the duration of response and PSA declines are less in the patients who received prior enzalutamide.

Decrease in the duration of response and rates of PSA decline with sequential therapies targeting the AR pathway suggest