Trastuzumab beyond progression: a challenge to translational oncology?

Anyone would find it a very unrewarding task to try to debate the fact that trastuzumab is probably the drug that has beaten most records in the recent history of oncology. When the drug was licensed in 1998 for use in pretreated human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer patients, trastuzumab was the first novel biological anticancer agent to be available for clinical use in a solid malignancy. The first steps of trastuzumab on the way to the glory were not so triumphal though. Initial clinical data did not appear as promising as it would prove to be at a later date, and it might have been dismissed as a mere pharmacological curiosity with minimal impact on clinical practice. As a single agent, it produced no more than 11.6% of overall response rate in heavily pretreated HER2-positive metastatic breast cancer patients [1] and very little was known then about the biological role and clinical relevance of HER2 as a crucial therapeutic target in breast cancer. Only a small portion of breast cancers all over the world was routinely tested for HER2 before 2000, and most of them were in major institutions with research activities. It does seem very strange that this was the actual situation slightly more than 10 years ago, but this is another of peculiarities in trastuzumab story.

When combined with first-line chemotherapy with taxanes, paclitaxel and docetaxel, trastuzumab started showing its potential [2, 3] and subsequently a large number of smaller phase II trials and retrospective studies of trastuzumab in combination either with single agent (vinorelbine, gemcitabine, capecitabine) or combination chemotherapy (taxane–capecitabine, taxane–vinorelbine, taxane–(liposomal) anthracycline, vinorelbine–capecitabine, carboplatin–gemcitabine) were published. So far, no final results from phase III trials comparing two or more trastuzumab-based chemotherapy regimens in the first-line setting have been published.

With the ensuing approval for use in the adjuvant setting for HER2-positive early breast cancer in 2006, trastuzumab broke yet another record and became the first monoclonal antibody licensed for use in an adjuvant treatment program of a human neoplasm. This happened only 8 years since its first approval in the metastatic setting, a surprisingly short time for an agent with such an innovative mechanism of action. Swiftly new important issues came to the attention of the oncology community. In view of its pioneering role in translational research that started a decade ago, trastuzumab forced oncologists to face new and unexpected problems that emerged with the new targeted anticancer agents: duration of treatment and role of treatments beyond progression, individuation of predictive factor of response/resistance, unexpected toxic effects, assessment of response, and costs sustainability.

At this point, we need to focus on another trastuzumab record that challenged the previously regarded paradigm of switching drug therapy on progression of disease to a subsequent line of a noncross-resisting treatment. This paradigm, highly regarded by generations of medical oncologists since the very beginning of use of cytotoxic therapies for cancer, has obviously some exceptions and special cases, but there is no doubt that trastuzumab has induced oncologists to a much different approach to the problem. More recently, there has been a progressively increasing trend in the practice of using trastuzumab beyond progression in first-line taxane-based chemotherapy. In most cases, it is given in combination with many different antineoplastic drugs; vinorelbine, capecitabine, platinum-compounds and gemcitabine being the most used. This practice has been commonly referred to as the ‘beyond progression’ strategy of trastuzumab therapy. The use of one specific combination instead of another is based in most cases on data from retrospective studies as well as empirical experiences of the treating physician. Many factors indeed may have contributed to this practice and they include the lack for many years of other agents targeting HER2, the data from in vitro combination essays of trastuzumab with different classes of cytotoxic agents, the favorable toxicity profile of trastuzumab, and not last the oncologists reluctance to renounce to such an effective drug as trastuzumab for HER2-positive breast cancer even in front of the evidence of disease progression.

It is very surprising that the practice of switching only the chemotherapy agent paired with trastuzumab at the time of progression on a trastuzumab-containing regimen anticipated by a number of years the first published prospective clinical trial specifically addressing this point. And we cannot say that this was due to a lack of scientific interest on this particular topic. In fact, in addition to the only prospective trial published, at least five other multicentric randomized clinical trials (three phase III and two phase II) both in Europe and in the United States result to have been registered on clinicaltrials.gov between 2004 and 2007 to specifically address the impact of adding trastuzumab to second-line chemotherapy in HER2-positive metastatic breast cancer patients who progressed on a first-line regimen including trastuzumab [4–8]. Two of these trials [7, 8] had a predefined second-line chemotherapy (vinorelbine or vinorelbine plus capecitabine, respectively), whereas in the other three trials [4–6] the chemotherapy associated with trastuzumab was left at the treating physician choice. The decision to permit the
physician’s discretion in deciding the type of chemotherapy to pair with trastuzumab was based on preclinical data showing various degrees of synergism with numerous cytotoxic agents other than paclitaxel and docetaxel and including vinorelbine, platinum compounds and gemcitabine. To the best of our knowledge, none of the above trials have completed enrolment as originally planned, and at least four of them have been suspended because of very slow recruitment and/or subsequent changes in second-line treatment options of HER2-positive breast cancer. Among the above trials, two were supported by large cooperative groups (Southwest Oncology Group, Grupo Español de Investigación en Cáncer de Mama) [7, 8], two were industry sponsored (Hoffmann-La Roche) [4, 5] and one was a study founded by a national drug authority (AIFA–Italian Drug Agency) [6].

In our own experience, coordinating the phase III TOP (Trastuzumab OPlimization) study [6], one of the five randomized clinical trials in this setting mentioned before, the support of AIFA did not avoid the premature termination of the trial when only <20% of study population had entered the trial in the entire planned accrual time. A similar experience occurred to the other trials with a design comparable to ours. In our opinion, this represents a strong message from the oncology community, which confirms that the use of trastuzumab beyond progression is something already established and well defined, despite the lack of definitive and unequivocal data from a phase III trial. Reflecting this practice, the only prospective clinical data available about the beyond-progression strategy for trastuzumab are those produced by GBG26/BIG03-05 trial from von Minckewitz et al. [9]. This study has the unquestionable merit to have attempted to answer this crucial question and today its results are consistently regarded as the proven evidence of the successfulness of that strategy. We are not going to discuss in details the GBG26/BIG03-05 trial that had already a number of comments, but we want to point out the fact that since its publication it has been used as the ultimate proof to ‘retrospectively’ legitimate a common practice that had a weak level of evidence.

There is no doubt that this is an unusual situation, a sort of methodological anomaly that is very far from being clarified in the next future with the current data we have, and it is possible that it will not be established ever at all. In fact, as everyone knows, a phase III trial is usually carried out to compare the current standard of care with another approach that could become the new standard of care in case of greater efficacy, better tolerability or both. Then, common practice follows the evidence from the phase III clinical trial if a significant difference was observed and if that difference was considered an improvement in the current standard of care. With the use of trastuzumab beyond progression, we are faced with the paradox of not having been able to perform an adequately powered and straightforward clinical trial that would require a few hundreds of patients to demonstrate the validity of this approach because in the oncology community there is the impression that this strategy has to be effective and does not need any formal confirmation. We are not saying that the beyond progression hypothesis cannot be correct but anyone can easily note the incongruence of this approach. And now that trastuzumab has been approved in combination with first-line chemotherapy for HER2-positive advanced gastric cancer, the same principles could be translated from breast cancer to other malignancies in which HER2 inhibition is considered crucial in pathogenesis and tumor progression. It is well known that the same approach has emerged with bevacizumab in metastatic colorectal cancer [10]. Even in this case, the beyond progression strategy has arisen doubts with the suggestion that so far findings from studies ‘must be interpreted as ‘hypothesis-generating’ and require confirmation in a randomized trial’ [11].

Things became even more complicated for breast cancer since the approval of lapatinib, a dual kinase (HER−1 and HER−2) inhibitor, in association with capecitabine in HER2-positive patients who progressed to trastuzumab and previously treated with an anthracycline and a taxane [12, 13]. There is no trial confronting head-to-head the second-line trastuzumab chemotherapy versus lapatinib–capecitabine, and any indirect comparison between the two trials would be methodologically inappropriate, even because of their differences in the sample size and patients’ characteristics. In view of the fact that the lapatinib–capecitabine study is an adequately powered trial it is reasonable to look at this combination as the standard second-line treatment of HER2-positive breast cancer. But, even in this case, the practice of resuming trastuzumab with a different cytotoxic drug has moved to the third or subsequent lines of treatment, in a setting where there is a nearly complete lack of data regarding activity and safety.

In fact, if one believes that maintaining a prolonged blockade on the HER2 signaling pathways is crucial for HER2-positive breast cancer throughout all the natural history of disease—and this should be clearly demonstrated in the pre-clinical setting first—it is not a matter of line of treatment anymore. And, if trastuzumab plus second-line chemotherapy is thought to be effective for the above reason, the very same kind of approach should be maintained in the third- or fourth-line setting. Results from the randomized phase II trial of lapatinib with or without trastuzumab in patients heavily pretreated with trastuzumab [14] show that the combination performed better than the single-agent approach (it would have been very interesting to design that trial with another arm with trastuzumab plus any chemotherapy as a sort of standard comparator!). A comprehensive discussion about this trial would take too long, but here we can just take the suggestion that molecular mechanisms of resistance may play a crucial role in response to therapies targeting HER2 in patients who were already pretreated with several lines of trastuzumab. Incidentally, it is interesting to note that patients enrolled in that trial had received a median of three prior trastuzumab-containing regimens.

Looking at the data we have from preclinical studies, it is noteworthy that in the works by Pegram et al. [15], fluoropyrimidines (including both 5-fluorouracil and capecitabine) were the only tested cytotoxic drugs not to be synergistic with trastuzumab or rather to show an antagonistic interaction. Interestingly, trastuzumab also failed to enhance growth inhibition mediated by vinorelbine in a pool of HER2-positive cell lines with acquired resistance to trastuzumab [16]. More recently, in xenograft models of HER2-positive human breast cancer progressing in response to trastuzumab monotherapy, the combination of trastuzumab and taxanes or...
capcitabine showed significant antitumor activity in one of the two cell lines tested. It seems that the same results were not observed with capcitabine in the other cell line [17]. Even considering all the differences between cancer in humans and in vitro or xenograft models, it is easy to understand that the biological context of this study is likely to be much far from what is expected to happen in the clinical setting when most patients are treated with trastuzumab together with taxane chemotherapy from very early stage and eventually develop resistance to trastuzumab and chemotherapy. Furthermore, all those in vitro studies cannot put in the proper perspective the role of the host immune system that seems to play as a protagonist actor rather than a walking on character. So far, there are very few data about in vitro effects of trastuzumab on lapatinib-resistant cell lines.

As the routine use of trastuzumab beyond progression with second-line chemotherapy would involve a huge number of patients, the cost-effectiveness of this strategy is a problem of the highest relevance. This has a significant impact on public health system costs and a judicious allocation of resources is crucial, mostly in present recessionary times. In this issue of Annals of Oncology, Matter-Walstra et al. [18] present the results of a cost-utility analysis of the use of trastuzumab beyond progression with capcitabine in HER2-positive metastatic breast cancer. This article is the first to address this aspect of trastuzumab use and is definitely noteworthy. The first observation to be made is that clinical data used for the cost-effectiveness analysis come entirely from GBG26/BIG03-05 study which is, as well known, the only prospective trial to have been published in this setting but which also presents some limitations. First of all, GBG26/BIG03-05 recruited only ~32% of the planned patients (156 instead of 482) over nearly 4 years (about two times the original planned accrual time). Secondly, the responses to treatment were not independently assessed, thereby raising the possibility of bias. Another element to be taken into account in the analysis by Matter-Walstra et al. is that all the medical costs were assessed from the perspective of the Swiss health system. They also did not consider indirect costs of treatment. Overall, they carried out their analyses in a very accurate and comprehensive way, considering all most relevant variables and using appropriate statistical methods.

The authors found that administration of trastuzumab and capcitabine after progression under trastuzumab-containing chemotherapy does not fall within the limits of what is typically regarded as cost-effective. They point out that, as expected, additional costs are mainly due to the acquisition of trastuzumab with a minimal impact of the administration and treatment side-effects. Interestingly, they calculated that a reduction in cost of trastuzumab by 30%–60% would result in a significant change in the scenario with a much higher probability that treatment will fall below the willingness-to-pay threshold. There is also another aspect of the analysis by Matter-Walstra et al., which requires a further brief discussion. Despite being not cost-effective in absolute terms, if compared with some newer combinations such as first-line taxane chemotherapy plus bevacizumab for HER2-negative advanced breast cancers, results for beyond progression trastuzumab appear paradoxically to be even more favorable than that other regimen that have become a standard of care for the past couple of years [19]. It is also noteworthy to observe that it has been reported already that the addition of lapatinib to capcitabine in the same setting is not clearly cost-effective as well [20].

In addition to that, we are made aware of the fact that no cost-effectiveness thresholds have formally been defined in most of European countries. Despite being a matter of primary importance either from the medical and/or the public health perspective, it seems apparent that there is a significant lack of regulations regarding what should be regarded as cost-effective and the role that such criterion should have in the process leading to approval of new anticancer agents and most importantly in fixing their cost for the national health systems.

With a view to the future, we do believe that a general rethinking of the decision-making process is strongly needed. It is also reasonable to expect that the wide application both at national and European levels of an approach to this topic based on adequately performed cost-effectiveness analyses would have a positive impact on the rational allocation of resources for the national health systems.

In conclusion, 12 years following its first approval in breast cancer and an astonishing number of records beaten, trastuzumab still presents a number of dark sides, and many crucial aspects regarding its optimization in the clinical management remain unclear. This is even more surprising than the clinical results achieved if we consider the huge body of clinical trials carried out and the efforts made in the area of translational research. If we think of where we are now with the beyond progression strategy, we have to admit that there are more doubts than certainties. In an era of challenging all standards of oncological practice, the oncology community has closed ranks on this vital question. Although it has been possible to enroll thousands of patients in clinical trials in a few years, it is disappointing that it was not possible to complete even a single adequately powered prospective clinical trial in this setting. This would furnish the scientific community with clear and crucial results. And what role for Translational Research? It seems to have been very marginal and scarcely significant in this particular area so far. The combination of trastuzumab with capcitabine, e.g. is not based on any preclinical or translational evidence and despite all the attempts done to individuate the molecular events behind de novo and acquired resistance to trastuzumab, no predictor other than the mere HER2-overexpression or amplification has entered in clinical practice yet [21, 22]. Patients are still empirically treated following therapeutic algorithms based on sequences of drugs tested in different settings, irrespective of the biological variables among individuals and the more and more multifaceted HER2-positive disease.

What has been happening with the acceptance of trastuzumab beyond progression for the past few years is an example of how a ‘general feeling’ based on a weak level of evidence can induce the oncology community to indulge in a sort of ‘comfortable unproven evidence-based care’ and, more importantly, how it can become an obstacle in the conduction of prospective trials aimed to find that ‘proven evidence’ that should only count. In this context, the bottom question is how can we conjugate hypothesis-generating data from small
retrospective analyses of (probably highly selected) patients with the need for much more solid evidences to drive our decisions on large groups of individuals. At this point, oncologists should wonder whether by fully legitimating the beyond progression strategy, trastuzumab is beating the most noteworthy among all its records: to be the first of all biological agents to have challenged the principles on which translational oncology itself is based. The answer is not simple and probably a few more years are needed to achieve a clearer view of what direction the relationships between molecular oncology and clinical research are going to take. But because of its pioneering role in translational oncology, trastuzumab should be regarded as a sort of special laboratory where new opportunities of progress are investigated and new problems urge us to solve them. We should not forget that often the greatest improvements in the medical sciences were made retrospectively, reviewing what was unknown along the journey to progress. ‘Trastuzumab beyond progression’ the oncology community should first acknowledge that there is an answer required.

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**references**