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LETTER TO THE EDITOR

The burden of scientific progress: Growing inequalities in the delivery of cancer care

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Abstract
Novel targeted therapies are now a reality in oncology. The monoclonal antibodies trastuzumab, rituximab, cetuximab and bevacizumab have a proven benefit in both advanced and early stage cancers. Furthermore impressive new technologies such as gene profiling, circulating tumour cells and proteomics are becoming major tools for prognostic assessment and prediction of response to certain treatments. Whilst this is certainly good news for patients it comes at a price, many of these technologies are very expensive and may result in unprecedented inequalities in the delivery of cancer care. The largest impact may be on developing countries, but inequalities are starting to be felt in some developed nations. Strategies to tackle the resource implications need to be addressed alongside the development of these technologies.

Most readers would probably agree that we are reaching a turning point in oncology: it is likely that within the next few years, we might see a major breakthrough, with the novel technique of gene profiling. This may also be case of other innovative technologies, such as proteomics or circulating tumour cells. This may happen, for instance, in terms of prediction of response to certain treatments. In two pilot trials, tumour "gene signatures" have been shown to predict response to taxane-based therapy [1,2], though this will need validation in larger, prospective, randomised clinical trials. There is also some data suggesting that "gene signatures" may also be powerful predictors of outcome in patients with early stage cancer. Dutch researchers identified a signature pattern of 70 genes that could reliably predict the outcome of 295 patients with early breast cancer (EBC) [3]. This study also suggested that patients with EBC may be overtreated when their risk of relapse is assessed based on the classical histological/clinical criteria, as supported by the current guidelines. A similar study has been recently presented by another Dutch group [4], and data are also available in other tumour types [5,6]. Based on these preliminary but encouraging results, the BIG/EORTC are about to launch a pioneer project where EBC patients will be randomised to receive adjuvant treatment based on either histological/clinical findings or tumour "gene signature". If the obstacles created by the recent "European Union Directive for Clinical Trials" can be overcome, this trial might be able to clarify whether "gene profiling" may actually be a more reliable predictor of outcome in EBC. One similar trial is about to be initiated in North America.

This is obviously good news for patients, but some caveats must be considered. Although experience has shown that, in developed countries, most cancer centres will eventually be able to cope with the costs/need for highly specialised staff necessary for the introduction of new technologies into clinical practice, the increasing complexity of these technologies may result in unprecedented difficulties for smaller and/or more financially deprived health economies.

DNA microarray is one potential example. This technique, which is now on the way to becoming established as a major tool in the prognostic assessment and treatment of cancer, is currently available in only a few centres, mostly in developed countries. Probably, only a minority of these centres would be able to start using this technology in large scale, at least in the short or medium term. The cost of an ordinary "GeneChip" including required reagents, for instance, is in the range of USD 1000–1500,

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which seems irrelevant when compared to the costs of acquiring the necessary equipment (USD 350 000–400 000 for Affymetrix, for instance). There are also further costs from equipment maintenance to training of highly specialised staff. Furthermore, it is possible that the unfortunate patients who develop incurable disease will need more than a single "gene signature" (in other words, the use of several GeneChips) prior to any new line of therapy, in order to most accurately predict response to each of these treatments. Of note, DNA microarray is used here just as an example. We have to consider that simplified, disease-specific GeneChips may become available in the future and, hopefully, will help to bring costs down and make this technology more widely available.

Another important, and probably more urgent issue, is the situation of non-developed countries. In most of South America, for instance, National Health Services have so far been unable to cope with the costs of some important, well-established novelties like trastuzumab (Herceptin®), rituximab (Mabthera®) and, frequently, other important cytotoxic agents. In Brazil, for instance, 75% (136 million) of the population cannot afford private health insurances [7], and would normally not have access to any of the agents above. Nevertheless, it is hard to criticize policy-makers for not paying this bill: the monthly cost of a treatment with trastuzumab in that country is approximately USD 4500 (plus a further US 3000 if used in combination with docetaxel). Roughly speaking, these figures would be enough to properly feed about 300 and 500 people respectively, for one whole month [8], in a country where 11.4 million families (close to 40 million people) were declared in absolute poverty and included in President da Silva's "Fome Zero" (hunger zero) campaign [9]. Considering the estimated incidence of 49 000 cases of breast cancer in 2005 [10] (probably underestimated), there might exist at least 20 000 patients with metastatic breast cancer in that country. If 20% of those were Her-2 overexpressing/amplified, at a certain point in time around 4000 women would be expected to be receiving treatment with trastuzumab. This would result in a monthly bill of USD 20 million (only considering the cost of the drug), which would be sufficient to feed at least 1 300 000 people enrolled in the campaign, for one whole month.

Another interesting point, which has been little debated, is the role of the wealthy pharmaceutical companies in this scenario. It is understandable that these companies, who have been largely paying the bill of scientific progress in oncology, must have a return for their investments. However, in light of the scenario above, is it reasonable to charge non-developed countries for this bill? Those readers who have previously worked on both sides will probably agree that cancer patients from countries with limited resources will always clamour for the best treatment, irrespective of cultural background. Like their wealthier counterparts, they will also fight for the 3–5 months disease-free survival and 5–8 months survival gain seen in the pivotal trials with addition of trastuzumab to paclitaxel and docetaxel [11,12]. Of note, Latin American countries are mostly wealthier than many African and some Asian countries, where the situation is likely to be worse.

Interestingly, several developed countries, particularly those relying on tax-based funding for health care (i.e. based on the principle of equality of health care for all its citizens), also seem to be experiencing their own difficulties. One good example is the case of the novel monoclonal antibodies cetuximab and bevacizumab: despite having been recently granted marketing authorisation within the European Union (for use in metastatic colorectal cancer [MCC]) and being supported by most clinical guidelines [13], very few EU countries have made these costly compounds available for use in daily practice. Furthermore, as of the date of submission, newer cytotoxics such as oxaliplatin and irinotecan were still unavailable for use as first line therapy for MCC in countries like the United Kingdom (despite level I evidence!).

In summary, the gap between poor and rich countries is widening faster than ever. Sadly, this is also resulting in growing inequalities in the delivery of cancer care. The increasing complexity and costs of high-tech developments are likely to make this gap even greater, and this may also affect more deprived populations, and even health districts within developed countries. The goal of this paper is obviously not to question or discourage scientific progress, but to encourage more discussion on potential ways to palliate such injustices. I also raise the issue of the role of renowned international societies like ESMO and American Society of Clinical Oncology (ASCO) in leading these discussions. Currently, non-negligible proportions of their members are from non-developed countries, and regularly attend their annual meetings. ESMO has developed an interesting initiative, namely the "ESMO/Developing Nations Joint Symposium", though this is more scientifically focused. ASCO has also developed some similarly successful initiatives. However, this could be taken a step further: why not consider a satellite symposium/workshop, to be held during their annual/biannual meetings, specifically addressing this issue? This could be a unique opportunity for health care providers to express and defend the interests of cancer patients from countries with limited resources, to further discuss the role of the pharmaceutical industry in this scenario and build up pressure for more collaboration, and to discuss any further creative solutions that would almost certainly come up.

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