

available at www.sciencedirect.comjournal homepage: www.ejconline.com

Current Perspective

Multinational clinical trials in oncology and post-trial benefits for host countries: where do we stand?

Max S. Mano*, Daniela D. Rosa, Lissandra Dal Lago

Institut Jules Bordet, Unité d'Oncologie Médicale, Rue Héger-Bordet 01, 1000 Brussels, Belgium

ARTICLE INFO

Article history:

Received 10 February 2006

Accepted 28 February 2006

Available online 7 September 2006

Keywords:

International research

Drug costs

Developing countries

Health economies

ABSTRACT

International collaboration has undoubtedly played a key role in the extraordinary progress we have witnessed in some areas of oncology in recent years. It has allowed us, for instance, to design trials large enough to depict very small benefits, as well as high-quality trials in less incident types of cancer. For different reasons, developing countries have also shown growing interest in this international effort and have been participating in many international trials. However, the ever-growing costs of novel anti-cancer treatments and technologies have created unprecedented difficulties for health economies in developing countries. Although the issue of individual benefit for patients must also be taken into account, the actual benefit for their society may be minimal. This paper discusses the ethics of including patients from non-developed countries in clinical trials evaluating the role of treatments that are unlikely to be made available to them after the trial because of prohibitive costs. Upfront arrangements ensuring post-trial access to interventions that have been proven successful might be the best alternative to exclusion from the research.

© 2006 Elsevier Ltd. All rights reserved.

With rare exceptions, cancer trials have resulted in modest perceived benefits. In the last two decades, we understood that instead of multiple, small often single institution trials, we needed fewer, larger, usually multicentre trials. To achieve this, national collaborative groups were set up in many countries, which have subsequently merged with others to constitute a global network of scientific collaboration. This network has played a key role in the extraordinary progress we have witnessed in some areas of oncology; it has become possible, for instance, to design trials large enough to depict very small benefits, as well as high-quality trials in less incident types of cancer.

Interestingly, developing countries have shown growing interest in joining this international effort and have indeed been taking part in many multinational trials.¹ Several reasons for this can be identified immediately: there is a drive for scientific progress in these countries, where cancer is also becoming a major public health issue; there is a growing drive

for academic achievement among investigators; patients also want access to the best available treatment and, as previously shown,^{2,3} they are best treated within the context of a clinical trial; finally, there is financial interest particularly in case of industry-sponsored trials where investigator's fees tend to be more generous. In summary, these reasons do not appear much different from those behind the frantic activity in the field of cancer research observed in developed countries in recent years.

However, the ever-growing costs of novel anti-cancer treatments and technologies have created unprecedented difficulties for health economies in developing countries. This issue has been addressed extensively by other papers and will not be discussed further here.^{4–6} What is in question is the ethics of including patients from non-developed countries in clinical trials evaluating the role of costly treatments that are unlikely to be made available to them after the trial.

* Corresponding author. Tel.: +32 2 541 3111; fax: +32 2 541 3090.

E-mail address: max.mano@gmail.com (M.S. Mano).

0959-8049/\$ - see front matter © 2006 Elsevier Ltd. All rights reserved.

doi:10.1016/j.ejca.2006.02.028

We do not need to go back in time too far to observe a few examples. In 2001, we witnessed the publication of a landmark study that unquestionably demonstrated that the combination of the monoclonal antibody trastuzumab with paclitaxel improved survival in patients with Her-2 positive metastatic breast cancer.⁷ Similar results have been reported recently with docetaxel.⁸ Since then, trastuzumab has been available for this indication in virtually all developed countries. However, a more careful look at the situation in non-developed countries will show that trastuzumab is still unavailable in the public system in the vast majority of these countries.⁴ The situation may become even worse with the approval of trastuzumab in the adjuvant setting, where this compound is considered potentially curative instead of simply palliative treatment. Of note, in at least two of the four clinical trials evaluating the role of trastuzumab in early breast cancer,^{9,10} a significant proportion of patients were from non-developed countries. They have helped to boost recruitment and contributed to the swift results. Trastuzumab is used here simply as an example because of the unusually large benefits observed in these trials, but there are many others.⁴

To the best of our knowledge, the Good Clinical Practice (GCP) guidelines, which have been conceived with the aim of ensuring that clinical trials be conducted within strict ethical standards, do not specifically address the issue of future accessibility to the treatment being investigated. The Food and Drug Administration (FDA), on the other hand, specifically recommends 'Institutional Review Boards (IRB) should not consider possible long-range effects of applying knowledge gained in the research (i.e. effects of the research on public policies)'. Indeed, 'central national bodies', instead of IRBs, should probably be in charge of dealing with such complex issues. A few years ago, the National Bioethics Advisory Commission (NBAC) in the United States of America (USA) has also issued an important statement addressing most of the issues above.¹¹ In summary, the commission recommended that 'no population, particularly a vulnerable one, should be the focus of a research unless some of the potential benefits of the research will accrue to that group after the trial'; the statement also refers to issues of 'post-trial benefits': 'researchers and sponsors should make reasonable, good faith efforts before initiation of a trial to ensure continued access to all participants to interventions that have been proven effective'. Although these sensible recommendations could serve as a framework for an 'international statement', these issues may also need to be formally addressed by the GCP guidelines. Finally, the scope of the discussion is probably not limited to interventional studies; further conflicts will almost certainly arise from the growing participation of developing countries in translational research studies, mainly because of transport of biological material and data generated by such research across borders.

From a more individual perspective, in written informed consent patients are usually told that the aim of the research is to evaluate a treatment that may be potentially superior to the current standard, at least in trials investigating the role of novel compounds. This also implies that they or other patients may benefit from the treatment in the future. Although the issue of individual benefit must also be taken into account, the actual benefit for their society may be futile. In

other words, it is possible that only patients from wealthier economies, and the sponsor, will eventually benefit from the data generated by the research; this is somewhat difficult to conciliate with the information usually provided in the informed consent form.

The aim of this paper is certainly not to discourage participation of patients from non-developed countries in clinical trials: this should instead be encouraged. We must simply try and find ways to harmonise post-trial access to successful interventions. This might be possible with some form of international collaboration; this has been achieved, for instance, in the management of patients with HIV/AIDS. In the era of biological therapies (and it is hoped of larger perceived benefits), the issue of wider access to costly treatments might become one of our greatest challenges and may indeed extrapolate the field of science to involve society as a whole. It would be ethically unacceptable to see all the effort and investment made by international researchers turn into a handful of miracle drugs and new technologies available only to an increasingly lower number of patients.

Some interesting solutions have already been proposed, but may require tough political decisions, such as re-visiting issues of drug patents in non-developed countries.⁶ Issues of post-trial drug accessibility may need to be addressed early in the setting of clinical trials; prospective agreement between trial sponsors and regulatory national bodies may be the easiest way forward. This may be particularly important when trials are run in countries with financially deprived health economies.

Finally, it may be too early to say, but some pharmaceutical companies (which drive medical research at the present time) appear to be turning to non-developed countries, as this may be a more cost-effective way of developing their own products. This may be good news provided these countries do not become merely a production line.

Conflict of interest statement

None declared.

REFERENCES

1. Schwartzmann G, Ratain MJ, Cragg GM, et al. Anticancer drug discovery and development throughout the world. *J Clin Oncol* 2002;20(suppl 18):47S–59S.
2. Hebert-Croteau N, Brisson J, Lemaire J, Latreille J. The benefit of participating to clinical research. *Breast Cancer Res Treat* 2005;91(3):279–81.
3. Du Bois A, Rochon J, Lamparter C, Pfisterer J. AGO Organkommission OVAR Pfisterer. Pattern of care and impact of participation in clinical studies on the outcome in ovarian cancer. *Int J Gynecol Cancer* 2005;15(2):183–91.
4. Mano M. The burden of scientific progress: growing inequalities in the delivery of cancer care. *Acta Oncol* 2006;45(1):84–6.
5. Demonty G. Treatment guidelines for adjuvant breast cancer are moving toward double standards: one for the rich and one for the poor. *J Clin Oncol* 2005;23(36):9436–7.
6. Tirelli U, de Castro GJ, Awada A. Reimbursement of effective new anticancer agents: we should change the process to ensure wide access to patients. *Lancet Oncol* 2006;7(1):2–3.

7. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;**344**(11):783–92.
8. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005;**23**(19):4265–74.
9. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;**353**(16):1659–72.
10. Slamon D, Eiermann W, Robert N, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. San Antonio Breast Cancer Symposium, 8–11 December 2005 (abstr 1).
11. National Bioethics Advisory Committee (NBAC). Ethical and policy issues in international research: clinical trials in developing countries. April 30, 2001. Available from: www.bioethics.gov.