

THE STATEMENT OF BARCELONA

THE FUTURE OF BREAST CANCER RESEARCH IN DANGER **Michael Baum, Mary Buchanan, Jose Baselga, Luigi Cataliotti** **Jacek Jassem and Martine Piccart**

INTRODUCTION

This statement has been prepared by the scientific committee of the 3rd European breast cancer conference that was held in Barcelona from the 19th the 23rd March 2002. This follows an open debate by the participants of the conference at a plenary session on Saturday the 23rd March. The agenda for this discussion had been set by the scientific committee following private discussions where we recognised that there was a pan-European concern about the future of clinical and translational research for cancer in general and breast cancer in particular.

BREAST CANCER IN EUROPE

Breast cancer is the commonest malignancy amongst women in Europe and the commonest cause of death amongst women in their middle years, although in some parts of Europe, with increasing tobacco consumption carcinoma of the lung is beginning to catch up or even overtake breast cancer as a cause of premature death.

Currently there are 321,000 new cases of breast cancer diagnosed in Europe each year and this is associated with 124,000 deaths. The trends in age specific mortality across Europe demonstrate remarkable patterns.[1] These were discussed in detail at a special session set aside to consider the matter. The data were presented by Professor Sir Richard Peto, following which there were three separate talks attempting to explain the trends in mortality according to socio-economic and lifestyle changes, the stage of diagnosis and improvements in treatment.

Across most of Europe there has been a steep increase in age specific mortality from breast cancer from the early post-war years until the mid 1980's. This almost certainly can be accounted for by increasing prosperity as the steepness of the rise was determined by the baseline socio-economic deprivation in the late 1940's and early 1950's. In addition lifestyle changes whereby professional women have been postponing the age of first pregnancy could also account for some of the rise in incidence and mortality from the 1960's onwards. Mortality rates started to plateau in the mid 1980's and in many countries throughout Europe there has been a significant fall in age specific mortality between 1987 and the year 2000. The steepest fall, amounting to approximately 30% has been witnessed in the UK.[2]

Explanations for this fall in mortality are complex. It is difficult, if not impossible to explain any of this fall to socio-economic or lifestyle trends. Some could be attributed to early diagnosis as a result of the screening programmes which began to be introduced in the late 80's early 90's but they would not be expected to deliver their full potential before the late 90's. Nevertheless the breast cancer awareness programmes linked to mammographic screening may have encouraged many women to present with their disease at a clinically less advanced stage.



That aside there was a consensus that something like two thirds in breast cancer mortality since the late 1980's can be attributed to improvements in treatment. It can be no coincidence that the first world overview of adjuvant systemic therapy was presented to the scientific community in 1985 [3] and treatments such as tamoxifen for post-menopausal women and cytotoxic chemotherapy for pre-menopausal women were rapidly introduced at that stage, which explains why the fall in mortality has been witnessed across all age groups, not just the post-menopausal women who are involved in the screening programmes.

Following the 1985 world overview there have been an increasing number of multi-centre randomised controlled trials for the treatment of early breast cancer involving collaborative groups throughout Europe with results that continue to demonstrate modest but incremental improvements. If implemented these newer modalities of therapy should contribute to a continuing downward trend in mortality throughout Europe.

There are many exciting new agents and therapeutic strategies that are awaiting formal evaluation by means of the randomised controlled trial. Yet this very mechanism, which has proven the benefits of treatment in the past and contributed to at least two thirds of the fall in mortality over the last fifteen years, is under threat by well meaning but misguided bureaucratic challenges.

THE PROTECTION OF THE INDIVIDUAL PATIENT FROM ABUSE IS THE FIRST PRIORITY

There has been a long and tragic history of the abuse of human subjects in the name of medical science. This dates back to the Nazi war criminals and the Nuremberg trials. That so-called medical research was nothing other than torture and the "science" was so seriously flawed that even out of all this human suffering, nothing of worth can be retrieved [4]. To make sure that these tragedies will never happen again we have had a number of ethical guidelines pre-eminent amongst which is the Declaration of Helsinki of the World Health Organisation.

Added to that we must not forget the thalidomide tragedy, resulting from the inadequate testing of a drug with appalling consequences to new-born babies. Then again it is essential to protect patient's confidentiality, which might be at risk by the exchange of notes and clinical details necessary for the conduct of clinical trials and finally there have been some well publicised examples of scientific fraud, misleading the public and causing untold harm. The most high profile of these was the fraudulent trial of high dose chemotherapy in South Africa [5]

These unquestioned abuses of human subjects have to be defended against but there is always the danger that the entirely appropriate and well meaning structures, guidelines and ethical directives might have unintentional consequences in the future.

It is our concern that the over-reaction to abuses in the past has erected so many bureaucratic hurdles as to make the future conduct of legitimate clinical research exceedingly difficult or prohibitively expensive.

OBSTACLES TO PROGRESS

Perhaps the most obvious obstacle to progress for randomised controlled trials in the treatment of breast cancer is the process known as good clinical practice (GCP). Even the term GCP is sinister in the way it has hijacked the meaning of words to suit the bureaucratic needs. There is nothing about the process of “good clinical practice” that can be taken as guidelines for the practice of good clinical medicine. In other words GCP has Orwellian overtones suggestive of 1984 where the very meaning of words has been distorted as to make rational thinking impossible.

Its intention is to protect patient confidentiality, ensure that all the ethical imperatives have been adhered to and guarantee that no rare but important adverse side effects of a new therapy will be overlooked. No one can argue against these lofty ideals, but the reality in practice is making the conduct of clinical trials according to GCP principles very difficult for the academic community and prohibitively expensive unless interpreted liberally. We would therefore urge the regulatory authorities to constantly revisit these issues and accept that the process is far from perfect at present. No one would wish the “law of unintended consequences” to apply, so that the very control mechanisms to police clinical research end up in extinguishing the flame of progress.

ETHICAL CONTROL

No one would dispute that good ethics and good science must go hand in hand. The original declaration of Helsinki was noble in its intent but subsequent versions have tightened controls and made the informed consent procedures so threatening both to the patient and the scientist as to discourage recruitment of the large numbers of patients which are required for statistical confidence. No one would deny the ethical principle of autonomy and the right to self-determination but societies cannot expect to give individuals their rights without in return the individual shouldering their responsibilities.

It could be argued therefore that if patients in the future demand better treatments than those in the past there is a moral responsibility to act as equal partners with the clinical scientists in the quest for the cure for cancer. There is a price to pay for autonomy but it ignores responsibility and this can be calculated in terms of unnecessary loss of life from cancer in the future. [6]

The Ethics Committees themselves that have to interpret and administer the declaration and codes of conduct governing clinical research cannot be populated by individuals who are mere tokens. The study of medical ethics is a scholarly subject. It is not intuitive and those who are granted the privilege of serving on these committees also have the responsibility to acquaint themselves with the nature of disease, the principles of the scientific method and an understanding of the philosophical underpinning of medical ethics.

If these Ethics Committees (institutional review bodies) do not accept their responsibility to encourage the future of cancer research they can be perceived as obstacles to progress, carrying equal responsibility for unnecessary loss of life in the future, as those clinical scientists who have abused the trust of the public in the past.

TRANSLATIONAL RESEARCH

As we are entering the era of “molecular medicine”, it becomes a high priority to understand why some patients benefit from the therapies and some don't.

We now have in our hands new and very powerful tools, such as genomics and proteomics, that should greatly facilitate this task and lead to greatly improved treatment individualisation in a not too distant future.

But this dream will never become a reality if translational research is not “facilitated”: in other words, individual tumor profiles must be obtained in the context of clinical trials, analysed in the laboratory and correlated to clinical outcome.

The creation of this essential “link” between clinicians and laboratory scientists can only happen if 1) patients understand its importance for the advancement of patient-care, 2) physicians are encouraged – and not discouraged – to devote extra time and efforts in this direction and 3) governments give financial support to these initiatives, which will not always be viewed as serving the interests of the Pharmaceutical Industry and, therefore, are better financed through an independent channel.

A very constructive proposal from Europa Donna representatives and deserving to be examined in more details is to incorporate consent for any sound translational research, whether carried out today or several years from now, in the clinical trial consent form, as long as it does not involve germline mutation studies.

The practical implication for this would be a simplified consent procedure, while the very few patients not willing to have their tumours analysed would be allowed to express this disagreement in a written document.

THE WAY AHEAD

One of the most heartening aspects of the European breast cancer conferences starting with the first in Florence and culminating in the third in Barcelona, has been the emergence of Europa Donna, the European Breast Cancer Coalition as a force to be reckoned with. Led by their President Dr Mary Buchanan and Vice President, Stella Kyriakides, their representatives have demonstrated a willingness and enthusiasm to be advocates for clinical trials as well as advocates for the needs of individual patients. In return for their support they make the legitimate plea that the patients themselves should be seen as equal partners and stakeholders in the fight against breast cancer.

We have now reached a very important crossroad in the history of clinical research for breast cancer which will no doubt be reflected across the whole spectrum of malignant disease in the not too distant future. The sufferers themselves recognise that it is in their enlightened self-interest to take part in clinical trials because patients treated within clinical trials tend to do better than those treated outside [7]. In addition the Europa Donna advocates recognise that as they are beneficiaries of volunteers for clinical trials in the past, they should contribute to the advance of knowledge for the next generation, many of whom might be their own daughters.

It is therefore essential to build on the vision that emerged from the Barcelona Conference, to set up networks and partnership groups where the consumer could be involved in the design and the monitoring of the clinical trial as well as being passive subjects within the clinical trial. EUROPA DONNA is already advancing well along these lines and has gained further encouragement from the cooperation and enhanced acceptance at EBCC3.

To achieve this requires an education programme targeted at lay-women, concerning the nature of science and the nature of malignant disease. Such an educational programme must target the young as well as the middle aged.

A similar education programme must also be targeted on future members of ethics committees and institutional review bodies who will sit in judgment of the clinical scientists in the future. Last but not least the politicians who are directly or indirectly responsible for the bureaucracy governing drug development and drug registration must be taught to have a longer vision than the instant popularity they seek in anticipation of the next election. For a start those responsible for “good clinical practice” must revisit this hydra headed monster in order to determine how it can be trimmed down in order to facilitate clinical research, rather than impeding it. We believe that this can be achieved with absolutely no threat to the patient providing common sense is allowed to prevail.

CONCLUSION

In conclusion this declaration of Barcelona, once more commits the clinical scientific community within Europe to progress in the search for the cure for breast cancer. At every step on the way this quest must ensure the protection of the individual patient and guarantee that her needs are pre-eminent above and beyond the needs of the clinical trial itself. Yet at the same time we believe that it is in the enlightened self-interest of the individual patients to be associated with the clinical trial process and this is now recognised by the women’s advocacy groups themselves.

The way forward therefore is to build on the strengths of the past where Europe has led the world in the discovery of better treatments for carcinoma of the breast. At the same time we must recognize the dangers and obstacles to progress in the future. Many of these obstacles are self imposed and are the unintentional consequences of processes introduced to protect the patient from the abuses that were prevalent in the past.

To achieve this, education has to be the watchword and that is education of the lay public and the ethics committees as well as education of the next generation of clinical scientists.

The next watchword is partnership and this partnership must be more than lip service to an ideal but a genuine mutual respect between the clinical scientist, their patients and the politicians responsible for the bureaucracy governing the discovery and registration of new therapies. GCP like tax and death is inevitable in one form or another but this must not be perceived as an obstacle to progress and the funding for GCP should not make the cost of the clinical trial prohibitive. If necessary it should be funded through tax revenue from central government rather than being seen as a burden upon the clinical academic establishment and the cancer charities.

Perhaps part of the solution to many of these problems is contained within the words of Stella Kyriakides from her Europa Donna plenary lecture on Friday the 22nd March:

"Life with Breast Cancer has slowly acquired a new meaning- it is slowly being associated with having a voice, with learning to raise it effectively by asking the correct questions, by demanding to be given valid and informative answers, by working hand in hand with all involved, by having hope in new treatments, by remaining realistic about the seriousness of the disease, by not forgetting those who lose their lives to it, by looking into the future with hope.

There is no longer "a feeling of despair created by the imagination which pretends there is a future" as Dubois once said, there actually IS a future. A future that allows us to enjoy every moment at hand, that allows planning for millions of moments and thousands of days ahead.

I really am not sure that we are survivors - some of us are patients, some have had the experience - of one thing I am sure, all of us here today, in this Odyssey, must be and are, PARTNERS. PARTNERSHIP IS WHAT IS ACTUALLY EMBODIED IN THE ORGANISATION OF THIS CONFERENCE BY EORTC, EUSOMA and EUROPA DONNA.

So let us all work hand in hand, as partners, to make life with breast cancer acquire its real meaning, achieve its true potential and create a future for every person faced with this reality."

References:

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