Friday, 22 March 2002 **14:45–16:15**

SYMPOSIUM

The new challenges generated by the exponential growth of adjuvant clinical trials

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The new challenges generated by the exponential growth of adjuvant clinical trials: the current situation in Europe and its challenges for the clinician

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The number of adjuvant randomized clinical trials for breast cancer (B.C.) has grown exponentially over the last few years. This growth first started on the North American continent, with the setting up of the American Intergroup, which is a powerful and efficient umbrella provided to most U.S. groups involved in B.C. clinical trials and that stimulates collaboration among them.

The "rest of the world" followed with the creation in 1996 of the Breast International Group (BIG), a communications network enabling B.C. cooperative groups with centers in Europe, Australia, New Zealand, South America, Africa, Asia and Canada to collaborate closely in clinical trials. As of late 2001, seven "BIG" adjuvant studies with a target accrual of 21,150 women are ongoing or have recently closed accrual, while several are ready to launch.

Also new in B.C. research is the rapid, efficient and "ad hoc" establishment of a large number of centers all involved in the field and coming together as a "group" to conduct large clinical trials addressing questions: of interest the ATAC trial with the enrolment of more than 9000 women fits into this model.

These models of international collaboration in B.C. research should better serve the women whose lives are affected by this disease. Indeed:

(1) We have learned from our clinical trials conducted in the 1980s that *statistical power* is essential to identifying new therapies or strategies with an impact on B.C. mortality;

(2) The importance of predetermined *subset analyses* has been recognized as a way to discover predictive factors for response to individual treatments, and these analyses call for larger numbers of patients at the outset;

(3) With the rapidly increasing number of "targeted" drugs entering the clinical scene it is foreseeable that adjuvant trials will one day target only *subgroups* of the B.C. population having predetermined biological characteristics ... a situation not manageable without international cooperation.

This evolution, however, gives rise to a number of new challenges:

(a) *for clinical investigators:* preservation of a forum for the open exchange of ideas rather than control by a small committee of "leaders"; preservation of "scientific independence" from the Pharmaceutical Industry, sometimes at the cost of reduced funding for research; building efficient communication across countries and continents; solving problems related to different cultural and legal environments; initiating and conducting translational research linked to the large clinical trials

(b) *for the pharmaceutical industry:* finding a satisfactory way of collaborating with these new networks and gaining faith in their capacity to conduct registration trials according to the required quality standards

(c) *for the women* enrolled in these "MEGA" trials: having to make difficult decisions at the time of the disclosure of a positive but early interim analysis (example of the ATAC trial)

It is hoped that governments in Europe and the rest of the world will understand that funding for the infrastructure of these networks of dedicated investigators is in their primary interest and should become part of their Health Service budgets.

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Restructuring NCI-sponsored clinical trials in the USA

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For over 40 years, the Clinical Trials Cooperative Groups have conducted phase III treatment trials that have set the standard for much of the present practice of oncology in the U.S.A. Supported primarily via public funds from the National Cancer Institute, this system has served the country well. However, the system has had difficulty adapting to changes in scientific discovery and medical practice. Among the changes are: 1) many new drugs or devices are no longer developed solely by NCI, so that most often partnership with industry is required; 2) an increasing percentage of patients on Cooperative Group trials come from community rather than academic practices. Industry requires an efficient, streamlined development process while community physicians need uniform, simplified approaches to optimize their participation. Phase III Group protocols often take 1ndash;2 years from inception to activation while the accrual phase for large, phase III trials takes 4.5 yrs on average. To increase the Groups' competitiveness for new drugs and to enhance accrual, NCI has modified the process of scientific review and protocol development. Rather than reviewing complete protocols, Groups now submit concepts using a template form.

Concepts are reviewed by a disease-specific Concept Evaluation Panel, comprised of government and non-governmental experts, that meets monthly via customized, on-line review software (ePancl©). After concept approval, NCI regulatory and pharmaceutical staff works together to complete the final protocol within 60 days. To increase accrual and access to phase III trials, NCI created the Cancer Trials Support Unit (CTSU). The CTSU serves as a one-stop shop for all the clinical trials needs of an investigator. By maintaining a super-database of all Group members, the CTSU can accept enrollment and collect study data for all approved Group phase III trials. This allows members of one Group to participate in the trials of other Groups, when their Group doesn't have a trial available. It will soon allow non-Group members to participate in Group trials by registering with the CTSU. The CTSU also provides physicians with educational fact sheets for each protocol that explain the rationale for the study to patients and provide general information about clinical trials. To reduce the paperwork burden and speed up study analyses, the CTSU is developing an on-line data collection system via the Internet In addition, the CTSU handles reimbursement for investigators and coordinates audits for the Cooperative Group system. The changes described above are designed to make the U. S. Cooperative Group phase III trials more accessible to community-based oncologists and more streamlined to attract partners from industry.

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The new challenges for the pharmaceutical industry

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It has become clear over the past few years that the size of clinical trials in oncology has been inadequate to demonstrate the real and clinically relevant differences that exist between different therapies. As a result trials are now significantly larger than before. This has led to new ways of working for the industry, involving increasing collaboration between companies and external groups. In order for these collaborations to work well, it has been necessary to set up new organisational models. These involve a true partnership between a company and one or more collaborative group. There is a sharing of expertise and personnel, and steering groups are formed which represent all participants in a trial programme. In order for this to work well, there needs to be a strong legal framework, but also a high level of trust. In trials where this model has been used, recruitment of patients has usually been rapid, and with advanced planning, communication of the trial results has been managed in a manner acceptable to all parties. Regular contact and extensive discussion is necessary to prevent the emergence of differences of opinion, but current experience suggests that as adjuvant trials in breast cancer will continue to require large patient numbers, this new way of working will prove optimal to all concerned.

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The new challenges for the regulatory authorities

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It is only recently that adjuvant studies (AS) have been considered by regulatory authorities, with a number of unresolved questions.

(1) Endpoint: the Note for Guidance has put emphasis on DFS. Nevertheless with AS, the occurrence of competitive risks (late toxicities such as secondary malignancies and organ dysfunction) can favor event-free survival or fixed time survival. In any case, follow-up less than 3-5 years is probably too short.

(2) Comparator: while any validated adjuvant regimen can be considered, only the most efficient ones should be used.

(3) Surrogate markers: they might speed up AS. Yet, none is validated,

and the technology to assess some of them (bone marrow/circulating tumor cells, naked DNAÉ) can be sophisticated and uneasy to disseminate.

(4) Type of trials: in theory non inferiority trials, equivalence or superiority are all possible with the goal to decrease risks and treatment burden, to increase efficacy, to improve benefit/risk ratio. The latter ones should be favored knowing that some non inferiority trials are based on an absolute difference in DFS of 5-7%.

(5) Who should ask for this marketing application. In a number of cases the tested agent(s) will not have a marketing protection at the end of such trials thus not triggering pharmaceutical companies to apply. Some legal opportunities should be defined for Institutions, Learned Societies, Health Authorities to support such variations so as to limit off-label of agents, and to incorporate guidance for the use of an agent or combination in the adjuvant setting.

More than a challenge, AS in fact raise new questions for the Regulatory Agencies to address in the cancer field including approval of multidrug regimens.

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Primary systemic therapy in operable disease

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Pre- versus postoperative systemic treatment in operable disease

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Pre-operative or neoadjuvant chemotherapy as a therapeutic tool in primary operable breast cancer was introduced in the late seventies. While its role in locally advanced breast cancer has been firmly established, the value of pre-operative chemotherapy in early stage breast cancer is still uncertain. The rationale for the administration of systemic therapy before locoregional therapy was based upon three different premises; first, downstaging of the tumor, second, to improve prognosis by inhibiting surgery-induced tumor cell proliferation, and third, to test chemo-sensitivity of the tumor in situ. To study whether pre-operative chemotherapy results into better overall survival compared to postoperative chemotherapy in early breast cancer patients, the EORTC Breast Cancer Group conducted a randomised phase III trial (EORTC trial 10902) which randomised between four courses of FEC60 given pre-operatively or postoperatively.

In total, 7 randomised phase II / III trials have studied pre-operative chemotherapy versus postoperative chemotherapy in primary operable breast cancer. Tumor response rates ranged from 50% to 85% and patients with a pathological complete response did have an excellent prognosis. Although impressive tumour response rates have been documented, the data concerning the number of breast-conserving therapies vary widely between the respective trials. However, breast-conserving surgery as opposed to mastectomy in this setting appears to be safe, although there is a suggestion of a small increase in local recurrence rate as was demonstrated in the NSABP trial. Most important, data from these trials show that the use of pre-operative chemotherapy neither prolongs nor decreases overall or disease-free survival when compared with the same chemotherapy given postoperatively. However, the ability to assess tumor response may be a significant advantage in that it allows a further option of adjusting systemic treatment in apparently resistant tumours. Especially in combination with highly promising new techniques like microarray technology and high-throughput tissue arrays, pre-operative chemotherapy may prove very useful. Micoroarray technology enables the identification of the entire genomic activity of cells. In cancer, this will also allow the classification of individual tumours by their gene expression profiles and describe and predict therapeutic resistance and sensitivity patterns. Therefore, microarray technology offers a new and unique way to identify tumour characteristics, which may enable physicians to customise anticancer therapy for the individual early breast cancer patient. In addition, high-throughput tissue arrays accelerate studies correlating molecular in situ findings with clinico-pathological information. This technique will lead to a significant acceleration of the transition of basic research findings into clinical applications.

Future pre-operative chemotherapy trials therefore should include predictive factor studies comparing gene expression and protein expression profiles before and after chemotherapy.

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Primary systemic therapy in operable disease - The rationale of chemotherapy - Achievements, predictive and prognostic factors

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Over the last two decades, numerous clinical trials have shown that a significant proportion of patients with large operable tumors requiring mastectomy may benefit from breast conserving treatment after several cycles of neoadjuvant chemotherapy using conventional regimens with demonstrated efficacy (CMF, CAF, AC, FEC, etc). This approach is becoming accepted as safe, although it yields modest results with about 10% absolute increase in breast conservation. Randomized studies did not show any difference in survival over the mere conventional approach using similar postoperative systemic therapy. Objective remission rates differ substantially when they are evaluated according to clinical measurements or with various imaging techniques (mammography, echography, CT-scan, NMR), and do poorly correlate with pathological response. A complete pathology response, defined as the absence of residual invasive tumor at the primary site and in the axilla, is observed in a minority of patients (10 to 30%), and is the sole reliable predictor of improved survival. The optimal duration of neoadjuvant chemotherapy is unknown, but generally lasts for 12 up to 24 weeks, depending on the regimen used. It requires a close monitoring of response, in order to detect early progression (rare within 12 weeks). Locoregional treatment must follow and consists in surgery or surgery plus radiotherapy (mandatory after breast conservation).

The second generation trials currently running investigate newer drugs (taxanes, capecitabine), targeted and potentially synergistic regimens (e.g. trastuzumab plus chemotherapy in case of c-erb/B2 overexpression).

Newer imaging techniques allowing early prediction of response after one or two cycles of treatment like PET-scan (FDG or other tracers) are increasingly used to monitor response. More individualized systemic treatment with modulation of systemic postoperative therapy, according to the response observed during the neoadjuvant induction phase, represents probably the most promising approach, likely to improve survival.

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The role of endocrine therapy in this setting

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Tamoxifen as sole therapy in primary operable breast cancer was investigated in the late 1970s and the 1980s in several phase II trials, when the clinicians tried to avoid surgery in elderly or unfit patients. Essentially the studies demonstrated response rates of 30-70% in unselected patients, however long term local disease control was poor.

There have been a series of randomized trials in elderly patients with primary operable breast cancer. Two trials initiated in the early 1980s compared tamoxifen with surgery and another 3 trials compared tamoxifen with surgery followed by tamoxifen. All but one of the trials demonstrated that surgery either as sole initial therapy or followed by adjuvant endocrine therapy provides better local control than initial endocrine therapy alone, but none of the individual trials demonstrated survival differences. However, the power of the studies is small.

These studies have led to the initiation of studies of preoperative endocrine therapy, the major aim being to downstage the tumour and thereby to be able to offer breast conserving surgery to a larger proportion of the patients. These trials have used tamoxifen, fulvestrant and aromatase inhibitors as the endocrine agents. One large randomized trial has been published and demonstrated letrozole to be significantly superior to tamoxifen in clinical response rates (60% vs 41%) and frequency of breast conserving therapy (48% vs 36%).

Preoperative setting provides an optimal model for translational studies. Data from the letrozole versus tamoxifen study suggest that Erb-B1 and Erb-B2 measurements can be used to select the most efficient endocrine therapy in this setting.

The impact upon survival with preoperative endocrine therapy remains to be established.

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Local treatment – Challenges after primary therapy

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The main goals of primary chemotherapy (PC) are: 1) to gain a more effective local and distant control of the disease; 2) to decrease the size of the