may be indicated for life-prolonging treatment and symptom management in hormone-receptor poor tumors, in hormone-receptor rich tumors progressing during endocrine treatment and in the presence of life-threatening metastases, such as lymphangitic lung lesions. With the exception of life-threatening disease, single agent sequential treatment is preferable to combination chemotherapy due to lower risk of complications. Of special interest to elderly individuals are capecitabine, gemcitabine, vinorelbine, liposomal doxorubicin, weekly taxanes.

217 INVITED

Favoring empirical extrapolation from trials in younger postmenopausal women with breast cancer

Abstract not received.

218 INVITED

Favoring specific clinical research for elderly women

S. Monfardini[1], U. Basso[2]. [1]*Azienda Ospedaliera di Padova, Medical Oncology, Padova, Italy;* [2]*Azienda Ospedaliera di Padova, Medical Oncology, Padova, Italy*

Multidimensional geriatric assessment has been shown to significantly add information on elderly cancer patients to be entered in clinical trials, allowing their division into three gross categories:

1. fit patients, who may be treated as adult patients,
2. vulnerable patients, who should receive treatments adapted to their limited organ reserve and partially compromised functional status, and
3. frail patients, who are candidates to palliative cares only.

The high response rate with combination chemotherapy in advanced breast cancer is probably not worth the added toxicity in elderly vulnerable patients. No results from the usual combination chemotherapy regimens have been so far published in women older than 70 years. The preferred first step should be then that of conducting single agent phase II–III studies with the potential advantage of avoiding excessive toxicity. At progression the choice could be again that of testing a new non-crossresistant drug. The results with weekly docetaxel, weekly paclitaxel, gemcitabine and capecitabine need to be confirmed on a larger number of vulnerable patients, while vinorelbine has been already proven as an active and well tolerated drug. Another interesting anthracycline with reduced cardiotoxicity is liposomal doxorubicin, which has a good activity without excessive toxicity in adult patients with breast cancer, therefore specific studies addressed to older patients are warranted. The new monoclonal antibody trastuzumab should also be tested in old patients due to its mild toxicity, with the possible exception of cardiac effects if used with anthracyclines. No adjuvant chemotherapy regimen can be considered as standard in women older than 70 years, since the classical, but also the i.v. CMF every 3 weeks, can be administered in general only at a reduced dosage and have not been tested in the frame of controlled clinical trials specifically designed for unselected elderly patients. Retrospective studies on adjuvant chemotherapy have been showing that only a part of patients at risk are treated and in some of them adjuvant therapy has to be prematurely interrupted. The best design of clinical trials of adjuvant chemotherapy for elderly vulnerable patients could possibly compare single agents (liposomal doxorubicin, vinorelbine, capecitabine) versus no therapy.

Thursday, 18 March 2004 14:15–15:45

ROUND TABLE

Challenges for translational research

219 INVITED

Translational research – key to the understanding of clinical trials

P. Therasse. *EORTC Data Center, Brussels, Belgium*

The landscape for cancer research is profoundly different today from that only one decade ago. Basic science is moving rapidly and biotechnological revolutions in molecular targeting, profiling and immunology have completely modified the opportunities and concepts for cancer treatment. Following this rapid evolution the concept of translational research has been developed to characterize the process linking clinical research and sound laboratory experiments which are needed to validate the hypotheses emerging from basic and pre-clinical research. Translational research in early clinical trials (Phase I and II) is an integral aspect of the development of the new generation of cancer drugs as it is necessary to implement radically different clinical trial design and to validate new biological endpoints if the full potential of these new agents is to be realized. The "proof of principle with mechanistic analysis" strategy will allow optimisation of therapy from the beginning, and provide important feedback to pre-clinical drug developers. Translational research is also essential in late (phase III) clinical trials to identify prognostic and/or predictive factors that will help defining different patient populations that may benefit to differing degrees from new treatments, and thus provide further insight and refine clinical practice in a more and more patient-tailored approach.

However, the implementation of translational research as a key component of drug development and clinical research is complex and involves patients in various ways. Thereby it imposes some new ethical, legal, logistical and management constrains. Moreover translational research may require highly sophisticated machines, specific imaging techniques, biochemistry laboratories and imposes other infrastructural prerequisites, some of which should be in the direct vicinity of the clinical trial site. The usefulness of data generated along translational research projects is highly dependent on the quality of the assays and the availability of sufficient numbers of samples to conduct valid analyses. The most common sources of tissues for research are residual surgical material and blood removed in the course of diagnosis and treatment of disease. These have the greatest potential as research tools but the real integration of translational research into a routine research agenda still face a number of challenges which relate to ethics (commercial or non commercial research, how should a patient consent, confidentiality), regulations (responsibilities, transfer of material across countries, property of material and research findings, confidentiality), logistics (collection of tissue, storage of tissue, tumor banking), scientific (defining the priorities to use the tissue) and costs (who will pay and what are the implications).

220 INVITED

Women's involvement

D. O'Connell. *Europa Donna Ireland, Dublin 6, Ireland*

At its most basic women's involvement in translational research in breast cancer comes about because of each woman's cancer and because of the scientific need for research material. The involvement presents challenges on all sides. The woman is challenged by the cancer diagnosis itself and by decisions about treatment. The request to sign a consent form, perhaps asking for consent to unspecified future research, is a further challenge. The medical team also faces a number of challenges in this process, including the obligation to ensure that the woman is making a truly informed choice (rather than consent).

Challenges for scientists and health professionals include the areas of collaboration with women in the administration and conduct of translational research, effective communication, gaining trust, working with laws and guidelines, information giving, allowing time for real decision making.

Challenges for women are to inform themselves, to value research, to communicate their views, to participate in decision making, to be prepared to active participants in the translational research process.

There are also challenges for society – to support translational research, to support clinical trials and those who take part in them, to ensure that the dignity and rights of trial participants are maintained, to legislate for the proper conduct of trials, to ensure that people (and their families) are not discriminated against on genetic grounds.

221 INVITED

Challenges of translational research: legal aspects

C. Trouet. *Pharma.be, Brussels, Belgium*

Translational research may impose the collection of tumor tissue during the investigational treatment. The increasing possibilities for using tissues for research and the developments in genetics have made stored human biological materials as well very important. We will focus on the legal and ethical problems raised by tissue banking for translational research.

Using human biological materials raises a lot of legal and ethical questions (commercialization, protection of privacy of the source, implementation of informed consent, new findings, role of research ethics committees etc.). Research with human subjects and research with personal data is covered by detailed European regulation. The research use of human biological materials however has not been regulated in a detailed manner so far. On the EU level, there is the draft European Directive on human cells and tissues, but this text covers only the therapeutic use of cells and tissues, not research use. The EU directive on the legal protection of biotechnological inventions deals with the question of informed consent for tissue retrieval in an indirect manner. On the level of the Council of Europe, the European Convention on Human Rights and Biomedicine provides for two general articles, one covering the principle of non-commerciality, the other covering the informed consent principle. A draft instrument on the research use of stored tissue is on the agenda of a specific working group of the Council of Europe.

We will briefly indicate the major issues in retrieving tissues for future research use and in using existing tissue banks for translational research. The main focus will be on the implementation of the informed consent requirement.

Thursday, 18 March 2004 14:15–15:45

SYMPOSIUM

New developments in systemic adjuvant treatment

222 INVITED

Endocrine therapy

N.E. Davidson. *The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Room 409, Baltimore, USA*

For nearly 20 years, the selective estrogen receptor modulator, tamoxifen, has been the primary agent for adjuvant endocrine therapy for women with steroid receptor-positive breast cancer. New data over the last several years are now challenging this. Recent trials support the use of ovarian suppression/ablation approaches with or without tamoxifen in place of chemotherapy for some premenopausal women. A large randomized trial has established the short-term efficacy and safety of the aromatase inhibitor, anastrozole, in place of tamoxifen for postmenopausal women. A second trial has also supported a role for sequential endocrine therapy as it demonstrated improved short term outcomes for postmenopausal women who received the aromatase inhibitor, letrozole, after completion of five years of adjuvant tamoxifen. How and when to integrate these new findings into standard practice are topics of debate. Ongoing research is focused on the choice of endocrine approach, duration and sequence of therapy, identification of better predictive markers for response to hormone therapy, and evaluation of long-term risks and benefits.

223 INVITED

Dose dense chemotherapy for early stage breast cancer

C. Hudis. *Memorial Sloan Kettering Cancer Center, New York, USA*

Combination chemotherapy in the adjuvant setting reduces the risks of relapse and death for patients with invasive breast cancer and adds to the benefits obtained with hormonal treatments [1]. Standard chemotherapy regimens have generally included two or more drugs given over a period of 12 to 24 weeks or longer. In general, anthracycline-containing regimens are superior to those without these agents, treatments longer than six months are not advantageous, and very high dose-regimens – meaning those that require autologous stem cell support – have not proven significantly or consistently superior [2]. Against this background, the development of the taxanes in the 1990s was important because these drugs appeared to be non-cross resistant, had partially non-overlapping toxicities, and were highly active. Hence, many adjuvant therapy trials testing the value of taxanes were developed and are now providing information on their role. To date, nearly every adequately sized and adequately followed trial testing these agents (paclitaxel and docetaxel) in the adjuvant or neoadjuvant setting has been positive and a role for them is broadly accepted [3–8].

Optimizing chemotherapy requires providing the maximal possible benefit at an acceptable level of toxicity. Kinetic modeling suggests that for many drugs dose-escalation beyond a threshold may not be necessary, that combination therapy may sometimes merely add toxicity without benefit, and suggests that sequential treatment applications may provide all of the benefits of combination treatment without the risk of additive side effects [9–11]. By choosing sequential chemotherapy plans we are also able to consider alterations in schedule of administration designed to increase cell kill by diminishing the time between treatments when sensitive clones might re-grow. The availability of granulocyte-colony stimulating factor was critical to the development of this approach as myeloid toxicity is dose-limiting for many of the active agents for breast and other cancers [12].

CALGB 9741 was designed to put these theoretical concepts to the test in a clinically relevant setting. Post-operative patients with node-positive breast cancer were randomly assigned using a factorial design to answer two questions [13]. One concerned the relative value of sequential single agents using active doses of doxorubicin, paclitaxel, and cyclophosphamide compared to a more "conventional" doxorubicin plus cyclophosphamide ("AC") combination followed by paclitaxel. Every patient was to receive four treatments using the same dosing of each of the three drugs. At the first protocol-stipulated analysis point there was no difference for the two treatment schemes supporting the hypothesis that combination therapy is not necessarily superior to sequential single agents. The second question concerned dose-density. All 2005 patients were randomized to receive their assigned treatment regimen at standard 3 week intervals or, utilizing G-CSF support, 2 week intervals. Two week treatment intervals resulted in a statistically significant reductions in the risks of relapse and death, the primary and secondary endpoints of the study. Moreover, there was little or no increased toxicity seen with the increased dose-density. In some regards it was less toxic as it was associated with a reduction in the risk of hospitalization for neutropenic fever. Hence, in CALGB 9741 dose-dense treatment was shorter, safer, and more effective. Planned studies will attempt to build on these observations.

References

[1] E.B.C.T.C, G., *Polychemotherapy for early breast cancer: an overview of the randomised trials.* Lancet, 1998. **352**: p. 930–942.

[2] Berry, D.A., et al., *High-Dose Versus Standard Chemotherapy in Metastatic Breast Cancer: Comparison of Cancer and Leukemia Group B Trials With Data From the Autologous Blood and Marrow Transplant Registry.* J Clin Oncol, 2002. **20**(3): p. 743–750.

[3] Smith, I.C., et al., *Neoadjuvant Chemotherapy in Breast Cancer: Significantly Enhanced Response With Docetaxel.* J Clin Oncol, 2002. **20**(6): p. 1456–1466.

[4] Nabholtz, J., et al., *Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (BC) patients: interim analysis of the BCIRG 001 study.* Proc. Am Soc. Clin. Onc, 2002. **21**: abstr #141.

[5] Buzdar, A., et al., *Evaluation of Paclitaxel in adjuvant chemotherapy for patients with operable breast cancer: preliminary data of a prospective randomized trial.* Clin Cancer Res, 2002.

[6] Henderson, I., et al., *Improved disease-free (dfs) and overall survival (os) from the addition of sequential paclitaxel (t) but not from the escalation of doxorubicin (a) dose level in the adjuvant chemotherapy of patients (pts) with node-positive primary breast cancer (bc).*Proceedings ASCO, 1998. **17**: abstract 390a.

[7] NSABP, *The effect on primary tumor response of adding sequential Taxotere to Adriamycin and cyclophosphamide: preliminary results from NSABP Protocol B-27.* Breast Cancer Treatment Reports, 2001: Abstr #5.

[8] Mamounas, E., et al., *Paclitaxel (T) following doxorubicin/cyclophosphamide (AC) as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28.* Proc Am Soc Clin Onc, 2003: Abstr #12.

[9] Norton, L., et al., *Predicting the course of Gompertzian growth.* Nature, 1976. **264**: p. 542–545.

[10] Norton, L. and R. Simon, *Tumor size, sensitivity to therapy, and design of treatment schedules.* Cancer Treatment Reports, 1977. **61**(7): p. 1307–1315.

[11] Norton, L. and R. Simon, *The Norton-Simon hypothesis revisited.* Cancer Treatment Reports, 1986. **70**: p. 163–169.

[12] Gabrilove, J., et al., *Effect of granulocyte colony-stimulating factor on neutropenia associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium.* New England Journal of Medicine, 1988. **318**(22): p. 1414–1422.

[13] Citron, M.L., et al., *Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.* J Clin Oncol, 2003: JCO.2003.09.081.

224 INVITED

Optimal integration of chemo-endocrine treatment

M. Colleoni, A. Goldhirsch. *European Institute of Oncology, Department of Medicine, Milan, Italy*

Chemotherapy in association with (usually followed by) endocrine therapy are considered an appropriate treatment option in the adjuvant treatment of patients with endocrine responsive tumors. Combined chemoendocrine therapies with tamoxifen and an anthracycline-based regimen were proven to yield better disease-free survival than endocrine therapy alone in patients with ER-positive tumors. The combination of tamoxifen with CMF-type regimens was superior to tamoxifen alone in trials using the "classical" CMF regimen. Laboratory studies have demonstrated that chemotherapy cell kill was inhibited in the presence of tamoxifen. Results from Clinical Trials also suggested a negative interaction between cytotoxics (alkylating