haematological malignancies and solid tumours. PS was recently approved by the FDA for the treatment of refractory or relapsed multiple myeloma.

The maximum tolerated dose (MTD) of single agent PS is schedule-dependent, and the highest MTD is achieved the weekly schedule, for 4 weeks, followed by 14-day rest period, used in solid tumours.

Single agent PS has a manageable toxicity profile, with most common side effects being grade 1–2 nausea (62%), fatigue (54%), diarrhoea (48%), constipation (41%), thrombocytopenia (41%), pyrexia (36%), peripheral sensory neuropathy (PSN) (35%), vomiting (34%), and anorexia (30%). Anaemia and neutropenia may also occur. Grade 3 side effects were seen in about 60% of patients, with the most common being thrombocytopenia (27%), neutropenia (12%), fatigue (13%) and PSN (13%). Grade 4 side effects are rare and usually haematological (thrombocytopenia and neutropenia).

Although PS is active against BC cells lines, in vivo models and phase I clinical experience have not yet shown its efficacy in BC when used as single agent. However, both preclinical and clinical data have proven its important activity when combined with other agents, suggesting an additive or synergistic effect, and a potential role in overcoming resistance to CT. With particular relevance for BC, PS has been shown to be additive/synergistic with doxorubicin, docetaxel and trastuzumab.

The combination docetaxel + bortezomib is currently being evaluated in a phase I study in patients with advanced and/or metastatic BC previously treated with an anthracycline-containing regimen. *In vitro* and *in vivo* results showed additive cytotoxicity for the combination, with increased inhibition of cell proliferation and significant reduction in tumour growth; this additive result could be related to the common effects of both drugs in p27 and bcl-2 levels. PS stabilizes p27 levels, and docetaxel induces p27 mRNA; the induction of p27 by docetaxel is enhanced in the presence of PS and is schedule-dependent, being higher when PS is administered one hour after docetaxel. Both docetaxel and PS are active in bcl-2-expressing cells, since they both induce phosphorylation of bcl-2, which releases the pro-apoptotic protein Bax and thereby stimulates apoptosis. The preliminary results of this study were presented at the ASCO 2002 meeting and showed manageable toxicity and promising activity (55% of partial responses). The most feared side effect was PSN, which lead to the development of specific dose modification recommendations. Only one patient experienced grade 3 PSN and two patients discontinued treatment due to this adverse event.

With great potential in BC therapy is also the association of PS with endocrine therapy. The proteasome is the major proteolytic pathway of ER degradation, both after estrogenic and anti-estrogenic stimulus, although estradiol induces ER ubiquination, while pure antiestrogens apparently use an ubiquitin-independent mechanism. Proteasome inhibitors not only block ER degradation but also its transcriptional activity. Since ER is a substrate of the proteasome, PS could increase the amount of available receptors and, consequently, increase the efficacy of endocrine agents. However, whether these ER are normally functional is a matter of ongoing research.

Our group has been evaluating another potentially relevant association: PS + trastuzumab. The rationale for this combination lies in the common effects of both drugs on NFkB (inhibition of its activation) and p27 (increased nuclear levels). Furthermore, HER-2 is also a subtract of the proteasome and therefore PS could have an effect on HER-2 receptor levels. The preliminary results of our preclinical work were presented at the San Antonio Breast Cancer 2003 meeting, and showed that: **1)** The combination has a synergistic effect on induction of apoptosis *in vitro;* **2)** Synergy is linked to NFkB and P27 pathways and is closely related to the HER-2 status. The results suggested that, in the clinical setting, PS could not only increase the efficiency of trastuzumab in HER-2+++ tumours but also allow it to be active in HER-2++ tumours. These hypotheses are currently being evaluated in an ongoing phase I trial.

Ubiquitin-conjugating enzymes: Selectivity of proteolysis strongly depends on the exact combination of ubiquitin-conjugating and de-ubiquitinating enzymes present at a given time. Selectively targeting proteins for ubiquitination and degradation is one the avenues for current drug development. A key component of the Ubi-Prot pathway is the ubiquitin-ligase; the recent available information about the crystal structure this enzyme and its substrates is being used in an attempt to develop compounds that induce stabilization or degradation of proteins. Moreover, since ubiquitination enzymes are target-specific, inhibitors of each ubiquitin ligase enzyme can be a more specific way of targeting the Ubi-Prot pathway, and are the subject of ongoing research.

29 INVITED

How to integrate new therapies to our current strategies

L. Norton. *Memorial Sloan Kettering Cancer Center, New York, USA*

Advances in the management of cancer with drugs are due only in part to the discovery and development of chemicals capable of causing shrinkage of malignant tumors. Of equal importance are principles of therapy that guide the use of these agents in terms of dose level, schedule, duration of therapy, and combinations. Understanding the historical basis for these principles, and their evolution as conceptual and empirical evidence warrants, is critical for designing clinical trials seeking to optimize the use of new drugs, some of which have novel mechanisms of action. For example, most drugs in the past have been developed with attention to the idea that the primary defect in cancer is uncontrolled and hence excessive mitosis. New targets such as apoptosis and angiogenesis will therefore present new challenges in experimental design and analysis; failure to do so may result in the false rejection of active agents. Similarly, the belief that the primary growth pattern of cancer is exponential has led to almost universally-held therapeutic principles that may not be applicable to the Gompertzian pattern more typical of human solid tumors. Examples are the use of drugs at their maximum tolerated dose within a multi-drug combination, administered in equally-spaced cycles of equal intensity. In contrast, mathematical modelling has long suggested that sequential use of single agents or smaller combinations would for certain tumor types preserve efficacy (especially by allowing maximally-effective dose levels to be used) while minimizing toxicity. Recent clinical trial data has supported this view, particularly in the adjuvant chemotherapy of primary breast cancer. The practical implications of this discovery are significant in that new agents may be added sequentially to existing regimens, avoiding the costly and cumbersome necessity of designing tolerable simultaneous combinations. In addition, as had been predicted by mathematical analysis, schedule has proven as important as dose in optimizing results. The post-operative administration of standard adjuvant drugs in two-week rather than three-week cycles has been shown to decrease the annual odds of death from breast cancer by more than 30%. Currently, the etiology of Gompertzian growth has been explored by the fractal geometric analysis of human breast cancer specimens. This work is leading toward a new, quantitative understanding of growth, both malignant and normal. The goal of this research is to identify new targets for anti-cancer intervention and new principles to direct their correct utilization.

Wednesday, 17 March 2004 14:15–15:45

SYMPOSIUM

Controversial issues in radiotherapy

30 INVITED

Adjuvant locoregional radiotherapy

P.M. Poortmans. *Dr. Bernard Verbeeten Instituut, Radiation Oncology, Tilburg, The Netherlands*

Radiotherapy, given after as well conservative as extensive risk-adapted surgery, reduces the risk of local recurrences by 2/3 to 3/4. Prognostic factors for local and regional recurrences include tumour size, the number of involved axillary lymph nodes and age. Based on this, radiotherapy is an integral part of breast-conserving treatment and is indicated after mastectomy for patients with more than four positive axillary lymph nodes, T3 and T4 tumour stages, invasion of the pectoral muscle, and invasion of surgical margins. However, the role of post-mastectomy and of regional radiotherapy for patients with an earlier tumour stage is unclear, whereas theoretically exactly those patients might benefit most on the survival endpoint because of their anticipated lower probability of spread beyond the regional lymphatics.

A meta-analysis of 40 randomised trials of postoperative radiotherapy demonstrated an improvement in overall survival of 3.9% at twenty years in the group of irradiated patients. Whereas the relative risk of breast cancer related death diminishes with 8.9%, this is partially counterbalanced by a relative increase of 18.2% of non-breast cancer related deaths, especially of vascular origin. A significant reduction in mortality was also found in a meta-analysis of 18 trials in women with node-positive breast cancer who received systemic treatment (odds ratio 0.83). The explanation of the observed reduction in breast cancer deaths remains unclear: the prevention of local recurrences through irradiation of the chest wall, the prevention of regional recurrences through irradiation of the lymph nodes, or both. Whereas the net effect of radiotherapy will strongly depend on the individual risk factors of the patient, it is of utmost importance to optimise the quality and set-up techniques of locoregional radiotherapy to avoid excessive exposure of especially lung and larger vessels.

The thin line between advantages and side effects of post-mastectomy and of regional radiotherapy for patients with an earlier tumour stage is currently under investigation by several ongoing well designed large prospective trials including EORTC 22922/10925, NCIC CTG MA.20, SWOG S9927 and PRIME. Large numbers of patients and a long follow up (at least 10 years) will be needed to answer the questions of these trials. Recent work on novel prognostic indicators, including DNA microarray analysis, opens new pathways to be explored; hopefully leading to tools

for tailoring adjuvant treatments to the individual cancer patient. In the meantime, adjuvant locoregional radiotherapy with appropriate radiotherapy techniques should be considered for patients having adverse risk factors.

31 INVITED

Partial breast irradiation

J. Bernier. *Servizio Oncologico Cantonale Ospedale San Giovanni, Radio-Oncology, Bellinzona, Switzerland*

Background: Breast conserving therapy (BCT) is the gold standard for patients presenting with early stage breast cancer. Post-operative radiotherapy nevertheless implies both a long overall treatment time, which can exceed 6 weeks – with all direct and indirect costs it imposes in terms of health economics – and, in some cases, a risk of post-radiotherapeutic complications or reduced cosmesis at the level of the whole breast.

Rationale for breast partial irradiation: The concept of partial breast irradiation was promoted by both surgeons and radiation oncologists, at first in patients aged 60+ and presenting with small T1 tumors. This subgroup of patients should indeed benefit the delivery of irradiation doses to a limited portion of the breast. It is assumed that the low risk of recurrence in other quadrants is likely to avoid any deleterious effect of partial irradiation on local control, with the advantage of sparing the rest of the gland, reducing the risk of late complications and increasing the quality of life.

Material and Methods: A first approach consists of an *intra-operative delivery* of irradiation using electron beams. Several approaches have been recently developed by various companies for intra-operative treatments: ELIOT, NOVAC-7, TARGIT, INTRABEAM and the treatment feasibility is now well documented. Mid-term results in terms of efficacy should be available within the next 12 months. In *post-operative setting* partial breast irradiation can be based on brachytherapy with doses reaching 32–34 Gy, when tumor presentation is compatible with a partial irradiation of the breast. In a very recent past, a new applicator (MammoSite®) has been developed to address these drawbacks of conventional brachytherapy techniques, allowing a more simple and reproducible radiation delivery to the target tissue area. This radionuclide delivery system is ideally inserted at the time of the surgical procedures, in order the balloon-shaped applicator fills up the cavity created by the tumor removal. With this system the overall treatment time is reduced from 6 weeks down to only 5 days, with all the advantages it implies in terms of logistics and direct/indirect costs for the patients. The role of intensity modulated radiation therapy in the field of partial breast irradiation is still investigational but this high conformality approach offers powerful tools that should allows an increase in total dose and a better sparing of normal tissues including lung, myocardium, and mammary gland tissue outside the target volume.

Results and Discussion: Preliminary results will be presented regarding treatment safety and efficacy will be presented for partial breast irradiation, in both peri- and post-operative settings. The discussion will be articulated around the advantages and limitations of this approach, as well as strategies aiming at an ultra-selection of patients according to their risk factors, disease pattern and treatment optimization tools.

32 INVITED

Altered fractionation schemes

J.R. Yarnold. *The Institute of Cancer Research, Academic Unit of Radiotherapy, Sutton, UK*

Radiotherapy regimens for women with early breast cancer based on 2.0 Gy fractions represent safe and effective approaches to patient management. They may, however, not be optimal. The results of a prospective randomised trial undertaken in Canada suggest that 16 fractions of 2.65 Gy are as safe and effective as 25 fractions of 2.0 Gy fractions in terms of local tumour control and late adverse effects [1]. Differences in overall treatment time between randomised groups make it difficult to take account of tumour cell repopulation in estimating the influence of fraction size on outcome. However, limited clinical data suggest that adenocarcinoma of the breast is significantly more sensitive to fraction size than squamous cell carcinoma of the head and neck, cervix uteri and lung, and may be as sensitive as the dose-limiting normal tissues of the breast. In a prospective randomised trial involving 1420 patients that compared two dose levels of a 13-fraction regimen (testing 3.0 Gy and 3.3 Gy fractions) delivered over 5 weeks against a control regimen of 50 Gy in 25 fractions in 5 weeks, the α/β value for late adverse effects (primary endpoint) was 3.6 Gy (95% CI 1.8–5.4) [2]. The point estimate of α/β for tumour control (secondary endpoint) was 4 Gy (no CI) [3]. The latter estimate is imprecise, but greater statistical power will be gained from 4450 women entered into the UK Standardisation of Radiotherapy (START) trial between 1998 and 2002 testing two 13-fraction schedules (testing 3.0 Gy and 3.2 Gy fractions) and 40 Gy in 15 daily fractions, against 50 Gy in 25 fractions. If the fractionation sensitivity of breast cancer is confirmed to be comparable to dose-limiting normal tissues of the breast and chest wall, there are potential benefits to be considered from hypofractionation with respect to tumour repopulation, scheduling with cytotoxic therapy, patient convenience and health services resource usage.

References

[1] Whelan, T., et al., Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst, 2002. 94(15): p. 1143–50.
[2] Yarnold, J.R., et al., Fraction sensitivity of change in breast appearance after radiotherapy for early breast cancer: long-term results of a randomised trial. 2002, Radiotherapy & Oncology: Praha, Czech Republic. p. S25.
[3] Owen, J.R., et al., Fractionation sensitivity of breast cancer: results of a randomised trial. 2003: ECCO, Copenhagen 2003.

33 INVITED

Timing of radiotherapy and chemotherapy

A. Fourquet. *Institut Curie, Dept. de Radiothérapie, Paris, France*

Combined treatment modalities with radiotherapy and chemotherapy result in lower locoregional and distant recurrences in patients at risk. Following conservative surgery or mastectomy, the relative risk reduction with radiotherapy averages 66%, whether patients receive adjuvant systemic treatment or not. This reduction in local recurrences result in a significant improvement in disease-specific survival.

Few data are available regarding the effects of timing or sequencing of chemotherapy and radiotherapy on the outcome of patients treated with primary surgery. Conclusions from retrospective studies are conflicting, but these studies suggest an increase rate of recurrence if this interval between surgery and radiotherapy is greater than 8 weeks when no chemotherapy is given, or greater than 6 months in patients who receive chemotherapy. Other studies suggest an increase rate of recurrence with increasing radiotherapy interval in subgroups at risk (i.e: with involved margins after breast-conserving surgery, or with involved axillary nodes). One randomised trial has compared two sequences, chemotherapy (4 cycles) followed by radiotherapy vs. radiotherapy followed by surgery, and show no differences in local or distant recurrence rates.

Recent trials have evaluate the effects of concurrent radiotherapy and chemotherapy and suggest some benefit in groups at risk.

In conclusion, few data are available on the effects of delaying radiotherapy or chemotherapy on outcome after surgery for breast cancer. An evaluation of the most effective sequencing of both treatment modalities must be considered in the design of upcoming trials.

Wednesday, 17 March 2004 14:15–15:45

SYMPOSIUM

Specific issues in early breast cancer related to very young women

34 INVITED

Genetics in very young patients

S. Delaloge. *Institut Gustave Roussy, Breast Cancer Unit and Genetics, Villejuif, France*

Epidemiologic characteristics and risk factors are slightly different in young breast cancer patients as compared to their older counterparts. Classical hormonal risk factors appear either to see their impact decrease with a decreasing age or to be inverted, while family history appear to have a relatively higher effect on risk. Despite these observations, germline deleterious mutations of genes predisposing to breast cancer in an autosomal dominant manner remain rare among young or very young breast cancer patients. In population-based series published, the prevalence of BRCA1 and BRCA2 deleterious mutations among patients diagnosed with breast cancer at ages less than 36 to 40 years is respectively around 4–6% and 2–3%. These numbers, however, increase dramatically with either the presence of an Ashkenazi descent (16–25% BRCA1- and 8% BRCA2-positive), of a family history of breast or ovarian cancer (linear increase with the number of first/2nd degree relatives affected), or, as recently shown, with the bilateralism or even multifocality of breast cancer. Except a recent series describing four germline mutations in the p53 gene among patients diagnosed with breast cancer before 30, the search for mutations in other predisposing genes have not been helpful yet.