

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 by 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 ubiquitination, 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 NFκB (inhibition of its activation) and p27 (increased nuclear levels). Furthermore, HER-2 is also a substrate 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 NFκB 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 of 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 of 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.

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INVITED

How to integrate new therapies to our current strategies

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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 tumours. 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 tumours. 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

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INVITED

Adjuvant locoregional radiotherapy

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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