dose intensity was 25 mg/m^2/week and the median dose intensity (MDI) received was 23.2 mg/m^2/week with a median relative dose (MRD) of 0.93. Two patients (6.4%) showed CR,10 patients (32%) showed PR, which accounted for 38.7% of the objective response rate; 5 patients (16.1%) showed SD > 6 months; taking this patients into account, 54% showed clinical benefits; of the responders five have been treated with anthracycline and six have received only adjuvant chemotherapy; 14 patients (45.1) showed PD. The median time to progression was 36.2 weeks and the median survival time was 18 months.

Treatment was generally well tolerated. Five patients (16%) required delay of treatment for neutropenia. Four patients (12.9%) showed grade 2 of stomatitis; five patients (16%) showed grade 1 of fluid retention; 8 patients(25.8%) showed grade 1–2 of fatigue and 3 patients (9.6%) showed grade 1 alopecia. 3 patients (9.6%) with concomitant fluid retention and fatigue requiring dose reduction at 7th, 8th and 10th infusion (tab 2). Nail changes where uncommon (1 patient) and mild.

Conclusion: The data reported confirmed the efficacy of docetaxel in the treatment of advanced breast cancer; the more favourable toxicity profile than 3-weekly (myelodepression) and weekly (fatigue) schedule registered suggest that the two weeks schedule could be routinely administered in the elderly patients or in those patients with low performance status.

Thursday, 23 March 2006 16:00–16:45

POSTER SESSION

Targeted treatment

425 Poster

SU11248 (sunitinib malate) therapy in patients with refractory metastatic breast cancer: preliminary safety and efficacy results from a phase II study

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Introduction: SU11248 is an oral, multi-targeted tyrosine kinase inhibitor of multiple receptors important in signaling pathways fundamental to tumor growth and survival including PDGFR, VEGFR, KIT, and FLT3. Progression of breast cancer (BC) is dependent on angiogenesis, a process stimulated by autocrine and paracrine signaling involving VEGFR and PDGFR. Results are reported here from a phase II study of SU11248 monotherapy in patients (pts) with previously treated metastatic BC.

Methods: Female pts with unresectable histologically/cytologically confirmed breast adenocarcinoma received oral SU11248 (50 mg/day) for 28 days followed by 14 days off treatment to comprise a 6-week cyclical regimen. Toxicity-related dose reduction was permitted. Response rate was assessed every 2 cycles by RECIST and was the primary endpoint. A total sample size of 63 was required to identify a clinically meaningful ORR ⩾15% based on Simon's Minimax 2-stage design.

Results: A total of 64 pts (median age 51 years) were enrolled. The majority of pts, 83%, had visceral disease; 61% and 17% were ER+ and HER2+, respectively. Fifty-two pts had received prior adjuvant chemotherapy (anthracycline 90%, taxane 56%) and in the MBC setting 61 pts were previously treated with anthracycline (26%), taxane (69%), capecitabine (66%), vinorelbine (23%), platinum (16%), and gemcitabine (15%). Overall, patients received a median of three prior chemotherapy regimens. The most frequently reported non-hematological grade 2/3 adverse events (AEs) were fatigue (41% and 14%, respectively), diarrhea (20% and 6%, respectively), and nausea (16% and 8%, respectively). Most frequent grade 2/3 hematological AEs were neutropenia (27% and 34%, respectively; no cases of neutropenic fever), anemia (17% and 16%, respectively) and thrombocytopenia (16% and 3%, respectively). One grade 4 AE was reported (neutropenia, which did not result in neutropenic fever). Of the 58 pts who experienced AEs, 24 (38%) required toxicity-related dose-reduction and 34 (53%) required dose interruption. In all, seven pts (11%) achieved a partial response of between 11 and 32 weeks duration. A further three pts (5%) achieved stable disease for ⩾6 months.

Conclusions: SU11248 has significant single-agent activity and acceptable toxicity in pts with refractory MBC. Toxicity is manageable with dose reductions and/or interruptions. Future studies should include less heavily pre-treated pts and alternative dosing and combination regimens.

426 Poster

Curcumin potentiates effect mediated by paclitaxel in breast cancer: in vitro & in vivo study

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Cancer chemotherapeutic strategies should be devised to provide higher tumor response and lower toxicity. Paclitaxel is the best anticancer agents isolated from plants, but its major disadvantage is its dose-limiting toxicity. The molecular basis of resistance to paclitaxel is not well understood, although mounting evidence supports the role of constitutive activation of NF-κB and thereby affording protection against cell death. Curcumin has been shown to inhibit the growth of various cancer cells in vitro and in vivo without toxicity to normal cells. The antitumor effects of curcumin could be in part due to inactivation of NF-κB activity. We hypothesize that blocking NF-κB activity may augment paclitaxel cancer chemotherapy. In this study, we investigated whether the inactivation of NF-κB by curcumin would enhance the efficacy of paclitaxel for breast cancer in vitro and in vivo.

MDA 231 GFP breast cancer cells were treated with curcumin, paclitaxel, and paclitaxel and curcumin combination. MTT assay, apoptosis assay and IκBα western blot assay (NF-κB activity) were performed. Curcumin dose-dependently decreased tumor proliferation and increased tumor apoptosis. MDA 231 GFP breast cancer cells were treated with 10 nM paclitaxel, 1 μM curcumin, 10 nM paclitaxel and 1 μM curcumin combination. Paclitaxel induced activation of NF-κB, but curcumin did not, and curcumin restored the NF-κB activation induced by paclitaxel. The combination of 1 μM curcumin with 10 nM paclitaxel elicited significantly greater inhibition of cell growth compared with either agent alone. The combination treatment induced more apoptosis in MDA 231 GFP cells compared with single agents. Moreover, in experimental breast cancer murine model using MDA 231 GFP cells combination therapy with paclitaxel and curcumin significantly reduced tumor size and decreased tumor cell proliferation, increased apoptosis and decreased expression of MMP-9 (down stream of NF-κB signaling pathway) compared with either agent alone.

These results clearly suggest that curcumin combination, which inactivates NF-κB activity, may contribute to increased cell growth inhibition and apoptosis augmenting paclitaxel chemotherapy, which could be a novel strategy for the treatment of breast cancer.

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Modulation of target therapy by estradiol in tamoxifen-resistant breast cancer cells

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Tamoxifen has been used as a main hormonal agent not only for the treatment of breast cancer but also for the prevention of the disease. Tamoxifen resistance is the major obstacle in hormonal therapy for breast cancer and the development of resistance was reported to be associated with HER2 or EGFR. To overcome tamoxifen resistance, clinical trial with trastuzumab or ZD1839 is ongoing. We had established a tamoxifen-resistant cell line with T47D:A18 breast cancer cells by long-term treatment of tamoxifen (1 μM). The resistant cell, T47D:A18/4-OHT, showed significant changes from estrogen dependent to partially dependent in cell growth pattern and from negative to positive expression of HER2. In this study, trastuzumab, humanized monoclonal antibody to extracellular domain of HER2 receptor, and ZD1839, EGFR tyrosine kinase inhibitor, were applied to the resistant cell, and Cell growth assay was performed to investigate their effects on growth of tamoxifen resistant cells. The changes of HER2 expression was confirmed by Western blotting. In the results of growth assay, each of them showed inhibitory action on growth of T47D:A18/4-OHT cells, but no synergistic action by the combined treatment with tamoxifen. Treatment of estradiol (1 nM) alone showed promoting action on growth of T47D:A18/4-OHT cells, however, unexpectedly co-treatment of estradiol (1 nM) with trastuzumab or ZD1839 revealed additional inhibitions of T47D:A18/4-OHT cell growth. Taken together, estradiol showed different roles in regulation of tamoxifen-resistant T47D:A18/4-OHT breast cancer cells according to changes in growth factor receptor signaling. This fact might be a clue to overcome tamoxifen resistance in the treatment of breast cancer.