Thursday, 23 March 2006 16:00–16:45

POSTER SESSION

New drug development

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Improvement of breast cancer metastasis-free survival by anti c-Src therapy

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We investigated the effect of c-Src targeted therapy on the development of breast cancer metastases. Balb-c nu/nu mice were intracardiacally injected with human breast cancer cells MDA-MB-231 (MDA), or with MDA cells stably over-expressing c-Src wild type ($MDASrc^{WT}$) or kinase-dead dominant negative c-Src ($MDASrc^{DN}$). Incidence and progression of cachexia and mortality were similar after injection with MDA or $MDASrc^{WT}$ cells, whereas neither cachexia nor lethality was recorded in mice injected with $MDASrc^{DN}$ cells. Bone and visceral metastases from these latter cells were reduced relative to MDA and $MDASrc^{WT}$-injected mice. In mice injected with parental cells, an improved outcome was also obtained by pharmacological treatment with the c-Src inhibitor CGP76030 (100 mg/kg/day p.o.). Histological and histomorphometric examination of tibias injected with MDA-Src^{DN} cells showed smaller tumor mass and a reduced osteoclast number/bone surface compared to MDA and $MDASrc^{WT}$-injected counterparts. Tumor weight and volume of subcutaneous xenografts from $MDASrc^{WT}$ and $MDASrc^{DN}$ cells were higher and lower, respectively, than those from MDA cells and the expression of the proliferation marker Ki67 changed accordingly. In vitro, c-Src inhibition caused a concentration- and time-dependent reduction of MDA cell proliferation, adhesion, and migration. Treatment of bone marrow cultures with conditioned media (CM) from parental or transfected MDA cells stimulated osteoclast differentiation to similar levels, whereas only CM from MDA and $MDASrc^{WT}$ cells stimulated the transcription of the osteoclastogenic cytokines IL-6 and IL-1 beta in osteoblast primary cultures. Endothelial cell proliferation but nor migration nor invasion was increased after treatment with $MDASrc^{WT}$ CM relative to the other tumor CM, while c-Src inhibitor did not appear to affect endothelial cell activity. In conclusion, our data indicate a notable role for c-Src activity in the development of experimental breast cancer metastases, thus pointing to this kinase as a potential pharmacological target for the obtaining of metastasis-free survival of breast cancer patients.

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A Phase I, open label, dose-escalating study of the proteasome inhibitor PS-341 (VELCADE®) in combination with two schedules of trastuzumab, in patients with advanced breast cancer (ABC) that overexpresses HER-2

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Background: The ubiquitin proteasome pathway plays an important role in cell cycle regulation, cancer growth and metastatic spread and is a promising novel target for anti-cancer therapy. HER-2 receptor is degraded by the proteasome, which can thus regulate HER-2 levels. Bortezomib (PS-341, VELCADE®) is a highly specific inhibitor of the proteasome and represents the first agent of this class approved for clinical use. We report the preliminary results of a phase I trial initiated to determine the maximum tolerated dose (MTD) and tolerability of bortezomib in combination with trastuzumab as first-line treatment of HER-2-positive ABC.

Methods: Patients (pts) were treated with bortezomib (1.0–1.3 mg/m^2; days 1, 4, 8 & 11) and trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly (Group A – Hw) or 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks (Group B – H q3ws)). DLT was defined as febrile neutropenia, grade 4 neutropenia without fever that does not resolve within seven days, grade 4 thrombocytopenia and any $\geqslant$ grade 3 non-hematological toxicity, with the exception of inadequately treated nausea, vomiting and diarrhea.

Results: To date, 11 pts were included and 9 are evaluable. The median age is 51 years (range 35–80 years), median number of metastatic sites 1 (range 1–4; visceral metastases 55.5%), prior anthracycline therapy 55.5% and prior taxane therapy 11.1%.

Treatment: bortezomib 1.0 mg/m^2 + Hw (n = 4), bortezomib 1.3 mg/m^2 + Hw (n = 3), and bortezomib 1.0 mg/m^2 + H q3ws (n = 2). Median number of cycles is 4 (range 2–8 cycles). A DLT (grade 3 muscular pain) was seen in 1 pt treated with Hw and bortezomib 1.3 mg/m^2. This cohort is currently extended with 3 extra pts. Grade 2 nausea, vomiting, diarrhea, thrombocytopenia, and liver function alteration were seen in 2 pts. A papular cutaneous rash was seen in 3 pts, which required therapy with steroids and anti-histaminics. The most common side effect was grade 1–2 asthenia (66.6%). No cardiotoxicity was seen. At this time, 1 partial response (PR) and 8 progressive diseases (PD) were seen. Of the 8 pts with PD, 5 received a combination of CT + trastuzumab as 2nd line therapy (3 obtained stable disease-SD, 1 PD, 1 too early to evaluate); 1 received CT alone (with PD), and 1 trastuzumab alone (too early).

Conclusions: So far, data suggest good tolerability of the combination bortezomib + trastuzumab with no cardiotoxicity. Cutaneous rash and asthenia have been the most common side effects. Enrollment is ongoing and an updated data will be presented at the meeting.

Study grant provided by Johnson&Johnson/Millennium Pharmaceuticals.

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Identification of targeted therapies for basal-like breast tumors

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The basal-like subtype of human breast cancer is aggressive and shows poor patient outcomes. It also lacks expression of the estrogen receptor (ER) and HER2; therefore, cannot be treated with biological drugs that target these proteins. The only treatments for these patients are cytotoxic chemotherapy. Therapies are needed for basal-like tumors that include the use of a biologic agent and chemotherapy.

Analysis of gene expression for a set of drug targets across a breast tumor data set identified several potential targets for biologic agents. HER1 and squalene epoxidase (SQLE) were highly expressed in basal-like tumors and cell lines. HER1 is a receptor tyrosine kinase that induces signaling cascades affecting growth, adhesion, differentiation, and apoptosis. Several inhibitors of HER1 exist that have promising efficacy in other cancers. SQLE is part of the cholesterol biosynthesis pathway, which is necessary for dividing cells. A specific SQLE inhibitor is available (NB-598) and an HMG-CoA Reductase inhibitor (lovastatin) is available that targets the cholesterol pathway at an earlier step.

Using a panel of cell lines that model the basal-like and luminal subtypes, we determined their relative sensitivities to a HER1 inhibitor (gefitinib) and to two cholesterol pathway inhibitors (lovastatin, NB-598). The basal-like cells were at least two-fold more sensitive than the luminal cells to gefitinib. Although cell line differences were identified in response to cholesterol pathway inhibitors, subtype specific differences were not evident. The lack of a subtype-specific response may be partially explained by the fact that SQLE is also highly expressed in other breast cancer subtypes. Because biological drugs are rarely used alone, we also examined interactions between these inhibitors and the chemotherapeutics 5-fluorouracil, doxorubicin, carboplatin, and paclitaxel. Biologics combined with 5-fluorouracil were typically synergistic, while combinations with paclitaxel were typically antagonistic. Tumor-derived basal-like lines were more sensitive to carboplatin than immortalized human mammary epithelial lines or luminal tumor-derived lines. Moreover, carboplatin and gefitinib were highly synergistic at low doses in the basal-like subtype, suggesting a potential therapy for these tumors. These analyses identify combined biologic plus chemotherapy regimens that may be efficacious for basal-like patients.