614 POSTER

Potential of AG in the treatment of breast cancer

J. Stanslas[1], P.S. Liew[1], N. Iftikhar[1], C.P. Lee[1], S. Saad[2], N. Lajis[2], R.A. Robins[3], P. Loadman[4], M.C. Bibby[4]. [1] *Universiti Putra Malaysia, Faculty of Medicine and Health Sciences, Serdang, Malaysia;* [2] *Universiti Putra Malaysia, Institute of Bioscience, Serdang, Malaysia;* [3] *University of Nottingham, Molecular & Clinical Immunology, Nottingham, United Kingdom;* [4] *University of Bradford, Clinical Oncology, Bradford, United Kingdom*

Purpose: AG is a diterpenoid lactone, isolated from a local herb. In this study the antitumour potential of this agent was evaluated using in vitro and in vivo breast cancer models.

Methods: Human breast cancer cells, MCF-7 (hormone-dependent) and MDA-MB-231 (hormone-independent) were cultured in RPMI 1640 medium supplemented with foetal calf serum and penicillin-streptomycin. The cell killing property of AG was determined using the microculture tetrazolium (MTT) assay. Type(s) of cell death induced by AG was determined using two DNA-binding dyes, acridine-orange and propidium-iodide. Effect of AG on the cell cycle progression was determined using flow cytometry. The pharmacokinetics (plasma concentration and t1/2) of AG at various doses was carried out using NCR-Nu mice. The in vivo antitumour potential of AG was established using 6 - 8 weeks old NCR-Nu mice transplanted with MCF-7 tumour xenografts.

Results: AG displayed approximately a 4-fold selectivity in killing the hormone-dependent MCF-7 cells over the hormone-independent MDA-MB-231 cells. Generally, apoptosis seemed to be the main mode of cell death induced by AG in the sensitive MCF-7 cells. However, necrosis occurred when the cells were treated with high concentrations (30 - 100 microM) of AG. This agent induced a consistent G1-arrest in MCF-7 cells. A preliminary pharmacokinetics study showed that AG reaches maximum concentrations of 20 - 30 microM and has a half-life of 1.5 hr in the plasma of mice treated with 150 mg/kg of AG. Since the concentrations achieved in the plasma are effective in killing MCF-7 cells in vitro, a single dose of 200 mg/kg was administered (i.p) to nude mice transplanted with MCF-7 cells. AG clearly inhibited the growth MCF-7 tumours in mice for a period of 14 days.

Conclusion: The abilities of AG to selectively kill the hormone-dependent breast cancer cells in vitro and inhibit the growth of in vivo tumours, makes this compound an ideal candidate to be developed for the treatment of breast cancer, especially the hormone-dependent type.

615 POSTER

Survey of modalities of assessing and reporting toxicity in non-comparative prospective studies of chemotherapy in breast cancer

P. Maione[1], E. De Maio[1], M. Di Maio[1], A. Ottaiano[1], M. Pensabene[2], G. Di Lorenzo[2], A. Vernaglia Lombardi[2], C. Gallo[3], F. Perrone[1]. [1] *NCI, Clinical Trials Office, Naples, Italy;* [2] *University Federico II, Oncology, Naples, Italy;* [3] *Second University, Medical Statistics, Naples, Italy*

Purpose: To review how toxicity, a main end-point of phase II studies, is assessed and reported in published phase II chemotherapy trials in breast cancer.

Methods: A survey was performed by hand-searching studies published in seven distinguished journals between 1995 and 1999. All selected papers were independently evaluated with an ad- hoc study report form by two investigators. Descriptive statistics, contingency tables and the chi-square test were applied.

Results: Overall, 122 papers were found; 65.6% of the papers lacked a statistical study design. Planned modalities for assessment of toxicity were inadequately reported in 21.0% of the studies. The scheduling of assessment of haematological toxicity varied greatly. Toxicity was predominantly summarized 'per patient' (69.7%). Although overall the WHO scale was more frequently adopted (45.9%), the Common Toxicity Criteria (in different versions) was more frequent in studies published in journals with a high impact factor (p=0.001), in more recently initiated studies (p=0.03), sponsored studies (p=0.0006), and studies with an identifiable statistical design (p=0.006).

Conclusion: The wide diversity in modalities of toxicity assessment and reporting observed in this study suggests that the reliability of the body of published data on the toxicity of chemotherapy in breast cancer may be questionable. Current standards should be revised and harmonized so as to improve the reliability of such data.

616 POSTER

The influence of genistein on the growth of experimental mouse mammary cancer 16/C and on the effectiveness of treatment with cyclophosphamide

J. Wietrzyk[1], M. Mazurkiewicz[2], C. Radzikowski[1], A. Opolski[1]. [1] *Institute of Immunology and Experimental Therapy, Department of Tumor Immunology, Wroclaw, Poland;* [2] *Medical University School, Department of Oncology, Lublin, Poland*

Genistein, an isoflavonoid present in soy products, is a phytoestrogen exhibiting various biological activities. It has been shown to be an inhibitor of tyrosine kinase and topoisomerase II activity as well as of tumor angiogenesis. In addition, genistein induces cell differentiation, apoptosis, and DNA strand breakage in the propagated in vitro cells and may reveal some estrogenic or anti-estrogenic properties.

The results of epidemiological studies suggest that the soybean consumption may contribute to the lower rate of breast cancers. Genistein was shown to inhibit the mammary tumorigenesis in rats, the proliferation and invasion of murine and human mammary cancer cells in vitro and the angiogenesis in human breast cancer cells xenografts.

The purpose of this study was to evaluate the antitumor effect of genistein alone and combined with cyclophosphamide in the mice transplanted with estrogen receptor-positive mouse mammary cancer 16/C. An influence of the route of tumor cells inoculation on the antitumor effect of these treatments and on the level of estrogen (ER) and progesterone (PgR) receptors was evaluated.

When genistein was administered from day 4th (during 10 days) after orthotopic tumor cells transplantation, the statistically significant stimulation of tumor growth was observed in the treated mice in comparison with untreated control group (3780 and 2834 mm3, respectively at day 24). Also in mice inoculated subcutaneously, stimulation of tumor growth by genistein was observed as compared to the control mice (2893 and 2540 mm3, respectively at day 27). After the treatment with CY alone or with genistein combined with CY, the statistically significant inhibition of primary tumor growth was observed in both s.c. and orthotopically inoculated mice.

On the other hand, in mice bearing s.c. tumors, genistein down-regulated the ER and PgR levels. No differences in these receptors level in mice transplanted orthotopically with 16/C tumor and treated or not with genistein were observed. In tumors from control mice transplanted s.c. the ER and PgR level was significantly higher than in tumors transplanted orthotopically.

In conclusion, genistein, known from its antitumor activity in some tumor models, stimulated 16/C mouse mammary cancer growth. On the other hand, in mice bearing 16/C tumor, genistein reduced ER and PgR level when the cells were injected s.c., but not after orthotopic transplantation of tumor cells.

617 POSTER

Primary chemotherapy, using outpatient (OP) continuous infusional (CI) 5-Fluoruracil, epirubicin and cyclophosphamide (IFEC), produces surgically significant down-staging in locally advanced breast cancer (LABC)

H.L. McCabe[1], U.S. Abdel-Hamid[2], A. Maraveyas[3], A.K. Modi[4], A. Chaturvedi[5]. [1] *Princess Royal Hospital, Academic Department Oncology, Hull, England;* [2] *Princess Royal Hospital, Department of Clinical Oncology, Hull, England;* [3] *Princess Royal Hospital, Academic Department Oncology, Hull, England;* [4] *Castle Hill Hospital, Department of Breast Surgery, Hull, England;* [5] *Princess Royal Hospital, Department of Clinical Oncology, Hull, England*

Introduction: In the neoadjuvant setting response rates (RR) of 75 to 80% have been reported. ECF regime (epirubicin, cisplatin and CI 5-FU) produces high RR, but is a toxic regime requiring hospitalisation. CI 5-FU alone in ABC produces (RR) of 20-30%, following failure of bolus 5-FU regimes. We describe our experience in treating women with LABC with OP primary IFEC (CI 5FU 200mg/m2/day, E 60mg/m2, C 600mg/m2, Q= 21 days).

Methods and Patients: From 1998-2000 chemo-naive women with histologically or cytologically confirmed breast cancer, inoperable (IO) or unwilling for mastectomy (M), were treated with IFEC (total 6 cycles if responding). Staging was according to clinical assessment, triple assessment (histology, mammogram and ultrasound), and metastatic screening (CXR or CTScan, and bone scan). Responses and toxicity were graded according to WHO criteria.

Results: 33 women,(with 34 tumours), age range 29-71 (2 <30yrs, 1= 30-40yrs, 14 =40-50yrs, 10=50-60yrs, 6 >60yrs), PS 0 (18) or 1 (15), received IFEC.14/34 tumours (41%) were T4, 12 (35%) were T3, 7 (21%)