1208 POSTER

### Long-term survival in a phase III randomised study of topotecan (T) vs paclitaxel (P) in advanced epithelial ovarian carcinoma

G. Ross[1], S. Lane[2], G. Dane[1]. *For the International Topotecan Study Group; [1] GlaxoSmithKline, Harlow, Essex, UK; [2] GlaxoSmithKline, Collegeville, PA, USA*

**Purpose:** We have continued to monitor the survival of patients randomised in a previously reported multicentre, randomised phase III study of topotecan vs paclitaxel in patients with advanced epithelial ovarian carcinoma who had failed one prior platinum-based regime (1, 2).

**Methods:** Patients with bidimensionally measurable disease were randomised to topotecan (1.5 mg/m2/day dx5) or paclitaxel (175 mg/m2/day as a 3-hour infusion) q 21 days. Patients were eligible for treatment with the alternate therapy at third line and these results have recently been published (3).

**Results:** A total of 226 patients were evaluable for response. As previously reported, the demographic characteristics were similar in both treatment groups. The EORTC QOL-C30 questionnaire was also used to measure eight symptoms at baseline and during each course (pain, anorexia, diarrhoea, fatigue, N/V, dyspnea, constipation, and insomnia); the results were similar. Time-to-progression was 18.9 wks in the topotecan group (range <1-92.6+ wks; 25% censored) and 14.7 in the paclitaxel group (range <1-137.3+ wks; 12.3% censored) (P=0.076). Survival was 63.0 wks in the topotecan group (range <1-238.4+ wks; 20.5% censored) and 53.0 wks in the paclitaxel group (range: <1-226.3+ wks; 12.3% censored) (P=0.438). Both treatment arms continue to provide long-term survival benefit. While the median survival remains constant, 20% of topotecan patients and 12% of paclitaxel patients remain alive at least 4 years after randomisation. The survival curves for topotecan and paclitaxel will be presented at the meeting.

**Conclusion:** Topotecan continues to demonstrate comparable efficacy and survival to paclitaxel with manageable and noncumulative hematologic toxicity. Non-haematological toxicity was generally mild for both groups. The long-term survival rate indicates substantial therapeutic benefit for this group of patients receiving therapy at relapse of ovarian carcinoma. (Supported by SmithKline Beecham)

#### References

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## Other gynaecological tumours

1209 POSTER

### Influence of anemia on tumor growth and tumor control- an investigation on advanced cervical cancers

G. Haensgen[1], U. Krause[2], S. Pigorsch[3], J. Dunst[4].
*[1] Martin-Luther-University, Radiotherapy, Halle, Germany;*
*[2] Martin-Luther-University, Pathology, Halle, Germany;*
*[3] Martin-Luther-University, Radiotherapy, Halle, Germany;*
*[4] Martin-Luther-University, Radiotherapy, Halle, Germany*

**Background:** The relationship between pre-treatment hemoglobin level and outcome is well-known in tumor patients. We investigated the correlation between pre-treatment hemoglobin, microvessel density (MVD) and the proliferation index on local response in advanced cervical cancer.

**Material and Methods:** The prospective study between 1995 - 1999 comprises of 87 patients with advanced cervical cancer with FIGO stage IIB (19), IIIB (59) and IVA (9), who were treated by definitive radiotherapy (external beam and HDR-Afterloading) in curative intention. The tumorspecific 3-year-survival was analyzed dependend on tumorstage and pre-treatment hemoglobin as well as the hemoglobin level at 20 Gy. Prior to therapy biopsies were taken in 46 pts. and stained by immunohistochemistry with anti-CD31 for microvessel density. From the same biopsy investigations by flowcytometry were performed for S-phase-determination as an marker for proliferation. For data analysis SPSS 9.0 was used. Results: Stage IVA (FIGO) in comparison to stages IIB and IIIB (p=0.0012) and pre-treatment hemoglobin at a cut-off level of 11g/dl (p=0.0018) were revealed as independent significant prognostic factors. Concerning the microvessel density we found a worse 3-year-survival for patients with tumors with high microvessel density (median 128/10 HPF) 41+ 24% (n=24) in comparison to a low microvessel density 69 + 11% (n=22). The correlation for MVD was not significant p = 0.12. For hemoglobin level and microvessel density we could confirm a trend with p=0.08.In an multifactorial analysis a survival benefit (p<0.05) for non-anemic patients neither pre-treatment nor at 20 Gy (Hb>11g/dl) compared to patients with decreasing hemoglobin level over radiotherapy was found. Local tumor progression was seen frequently in patients with stage IVA (relative frequency 0.67) and in anemic patients (0.38 Hb< 11g/dl vs. 0.20 Hb> 11g/dl). Anemic patients showed a higher prolifaration rate with 25 + 16% versus 17 + 10% of cells in S-phase (p=0.059).

**Conclusion:** Tumor anemia worsens prognosis on local response in patients with advanced cervical cancer. Tumors with high proliferation rate are more common in anemic patients. The treatment of anemia may improve local response but does not promote aggressiveness of tumors.

1210 POSTER

### Transperineal low dose rate interstitial brachytherapy in the treatment of carcinoma of the uterine cervix. Long term results

A.A. Puthawala[1], A.M.N. Syed[1], P. Disaia[2], M. Berman[2], N.N. Abd-Elaziz[1], A. Londrc[1]. *[1] Long Beach Memorial Medical Center, Radiation Oncology, Long Beach, USA; [2] UCI Medical Center, GYN Oncology, Orange, USA*

**Purpose:** To evaluate the long term results of transperineal interstitial brachytherapy in the treatment of locoregionally advanced carcinoma of the uterine cervix.

**Materials and Methods:** Between 1977 and 1997, a total of 185 women with biopsy-confirmed carcinoma of the uterine cervix underwent definitive radiation therapy. All patients were staged using FIGO system. Stage IB (barrel) 21 (11%), stage IIA 9 (5%), IIB 68 (37%), IIIA 13 (7%), IIIB 64 (35%), IVA 8 (4%), and IVB 2 (1%). Majority of these patients were unsuitable for conventional intracavitary brachytherapy due to bulky disease, distorted anatomy, tumor extension to lower vagina or to pelvic wall with fixation. All patients were treated with a combination of external beam irradiation to the pelvis to a dose of 5040 cGy over 5* weeks time. A lower midline block was used after 3960 cGy. Two separate interstitial implants were performed at two week intervals delivering 20 to 25 Gy dose with each implant. The dose was typically prescribed to the entire implant volume with dose rate of 60 to 80 cGy per hour with MEAN implant dose to Point "A" of 25 Gy.

**Results:** The MEAN follow-up period for the entire group is 51 months (range 3 to 223 months). An initial local tumor control was achieved in 152/185 (82%) of patients. A sustained locoregional control was maintained in 73% (136/185) until the time of last follow-up or death. The five-year overall survival rate was 45% while five-year disease-free survival for the entire group was 58%. This has been broken down according to the FIGO stage 65%, 67%, 49%, and 17% for stage I, II, III and IV, respectively. Isolated distal metastasis developed in 28/185 (15%) of patients and 49 patients who failed locoregionally, 16 (33%) also developed distal metastatic disease. RTOG grade 1 & 2 GU and GI toxicity was self-limited to all patients and grade 3 acute toxicity was experienced by 32% of patients. The late grade 3 and 4 GU and GI complications occurred in 17/185 (9%) of patients requiring surgical intervention.

**Conclusion:** Transperineal interstitial brachytherapy is efficacious and safe for the patients with bulky and advanced cervical cancer who are not ideal candidates for conventional intracavitary brachytherapy.

1211 POSTER

### Tumor growth inhibition by antisense DNA methyltransferase oligonucleotide in cervical cancer

C.L. Chen, Sin-Ming Ip, Hextan Y.S. Ngan. *The University of Hong Kong, Obstetrics and Gynecology, Hong Kong, Hong Kong*

Cervical cancer is one of the most common female cancers worldwide. Apart from the involvement of HPV infection, many genetic and epigenetic changes are also play important roles in this cancer. DNA methylation (methylation in the CpG island of promoter site resulting in inactivation of tumor suppressor genes) and genomic imprinting (preferentially expression one of the parental original allele) are two important epigenetic events involved in many human cancers. So far, DNA methyltransferase (DNMT1)which has both maintainance and de novo methylation function is considered the important enzyme in these two epigenetic events. However, the role of DNMT1 in cervical cancer is not quite clear.

In this study, we first studied the imprinting status for two imprinting genes: IGF2, H19 genes as well as the methylation status of several tumor

suppressor genes in 5 cervical cancer cell lines. We found that one of the cell lines, SiHa demonstrated both loss of imprinting (LOI)of IGF2 and H19 as well as loss of E-cadherin protein expression due to DNA methylation. We further examined DNMT1 mRNA level and activity of the enzyme, and found that this enzyme was markedly elevated in this cell line as well as in cervical cancer tissues. We designed an antisense methyltransferase oligonucleotide in the initiating start site of this gene (20bp), modified with 2'-O-methyl and phophorothioate. A control oligo was also designed with 6 mismatch bases. The antisen oligo and control oligo were transfected into SiHa cell line, respectively in the presence of lipofectin. We found that LOI of both IGF2 and H19 can be reversed to normal imprinting status and the silenced E-cadherin protein was activated by the antisense oligo, not the control one. The tumor cell inhibition was found in three aspects in the antisense group: tumor cell growth was markely inhibited in cultured cells; tumor clonies formation in soft agar was also much less in antisense group and finally tumor formation in nude mice showed more than two times smaller in the antisense group.

These results suggest that antisense methyltransferase oligo can abrogate DNMT1 and inhibit cervical cancer growth through epigenetic regulation of some tumor suppressor genes as well as imprinting genes. So, we conclude that DNA methylation plays an important role in cervical cancer.

1212 POSTER

## A phase I-II study of weekly cisplatin (C) and gemcitabine (G) with concurrent radiotherapy (R) in locally advanced cervical cancer (LACC)

J. Zarba, A. Jaremtchuk, L. Cedaro, P. Gonzalez Jaley, M. Keropian, R. Castagnino, C. Mina. *GETICS (Grupo de Estudio, Tratamiento e investigacion del Cancer del Sur), Gynecology, Bahia Blanca, Argentine*

**Background:** Concurrent R and chemotherapy may be considered as the new standard treatment for LACC and weekly C is probabily the best option. G has modest activity in cervical cancer, however it is a potent radiosensitizer demonstrated in pre clinical and clinical studies in cervical cancer.

**Objectives:** Determinate the maximun tolerated dose (MTD)and the antitumor activity of G when is administrated in combination with concurrent C an R in LACC.

**Patients and Methods:** Patients (pts) with histologically confirmed LACC previously untreated, PS 0-2 and adecuate organ function were eligible for entry in the study. R was administrated at conventional doses and fields (50.4 Gy in 5 weeks). Concurrent, weekly chemotherapy was administrated with C 40 mg/m2 in 1 hour infusion and G in 30 min. infusion at increasing doses levels until find MTD.

**Results:** Therty-six pts were included between 7/99 and 3/01. In phase I, 16 pts were entered at four dose levels (75, 100, 125 and 150 mg/m2). The MTD was 150 mg/m2 and the recommended dose of G for phase II was 125 mg/m2. Twenty additional pts were entered at this level for a total of 26. Toxicity at the recommended dose was acceptable with grade 3-4 toxicity in less than 20% of pts and mostly non-hematologic. The combination was active in all dose levels. In total 29/36 pts were assessable for response, all pts achieved an objective response, 27 (93%) CR an 2 (7%) PR. At a median follow up of 12 months, 22/27 (81%) pts are in sustained CR and 7/29 (24%) relapsed, 4 within the radiation field and 3 outside (one lung and 2 bone metastases).

**Conclusion:** The association of weekly C and G with concurrent R if a promising two-drug regime in LACC, but its superiority or equivalence in terms of activity or toxicity, to other combination without G must be adressed in a randomized trial.

1213 POSTER

## Prognostic factors in endometrial carcinoma: the significance of the tumour grade

A.N. Scholten[1,2], C.L. Creutberg[1], E.M. Noordijk[1], V.T.H.B.M. Smit[2]. *[1] Leiden University Medical Center, Clinical Oncology, Leiden, The Netherlands; [2] Leiden University Medical Center, Pathology, Leiden, The Netherlands*

**Introduction:** Endometrial carcinoma is the most common malignancy of the female genital tract. Various pathological factors, such as tumour grade and myometrial invasion have been reported to have prognostic significance. Although the determination of these factors may seem clear and reproducible, recently the tumour grade has been subject of debate. We conducted a retrospective analysis of prognostic factors in endometrial carcinoma, focusing on the predictive value of tumour grade.

**Material and Methods:** The study included 253 patients with endometrial carcinoma stages I to III, treated between 1984 and 1993. The histological slides were reviewed and the prognostic value of tumour grade (FIGO 1988: 1-3), stage (I-III), age (< vs ≥ 60), depth (< 1/2 vs ≥ 1/2) and pattern (pushing border vs infiltrating) of myometrial invasion and histological subtype (adenocarcinoma vs other) were analyzed. The endpoint was cancer-specific survival (CSS). The median follow-up time was 11.7 years.

**Results:** The actuarial 5- and 10-year CSS rates were 85 and 82%, respectively. Five-year vaginal and/or pelvic recurrence and distant relapse rates were 7 and 15%, respectively. At pathology review, a shift from grade 2 to grade 1 was seen in 112 of the original 144 grades 2 (78%). There was no difference in CSS between grade 1 and grade 2 (94 vs 90% for original and 92 vs 95% for grade after review), while grade 3 was a significant adverse prognostic factor ($p<0.001$). Depth of myometrial invasion had no significant predictive value, in contrary to the pattern of invasion; a pushing border yielded a significantly better 5-year CSS compared to the infiltrating variant, 89 versus 80% ($p=0.02$). In multivariate analysis, stage, age and tumour grade were found to be independent prognostic factors.

**Conclusions:** The significant prognostic factors for patients with endometrial cancer were tumour grade, myometrial invasion, stage and age. For myometrial invasion, we found the pattern of invasion to have significant prognostic power, rather than the depth of invasion. Tumour grade 2 appeared to have little reproducibility and little distinctive value as compared to grade 1. Therefore, we propose a 2-tiered grading system in stead of the currently used 3-tiered system, since it will have less inter-observer variability and a better correlation with clinical outcome.

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## Irinotecan and cisplatin as first line chemotherapy in metastatic or recurrent cervical cancer

I. Chitapanarux, V. Lorvidhaya, A. Tonusin, V. Sukthomya, C. Charuchinda, N. Pukanhaphan. *Chiangmai University, Division of Therapeutic Radiology and Oncology, Chiangmai, Thailand*

**Purpose:** The combination of Irinotecan and Cisplatin has shown synergism in many clinical studies. We conducted a phase II study to evaluate the efficacy and tolerability of this combination in patients with metastatic or recurrent cervical cancer.

**Method:** All patients had histologically proven cervical cancer with metastatic or recurrent disease, absence of prior chemotherapy and at least one measurable tumor site, 18-75 years old, adequate hematopoietic, renal and hepatic function. WHO performance status not more than 2. Prior radiotherapy had to complete more then1 year before study entry. Patients received Irinotecan as 90 minutes infusion of 60 mg/m2 on day 1, 8 and 15 in combination with cisplatin of 60 mg/m2 as 90 minutes infusion on completion of the Irinotecan infusion on day 1 every 28 days for a maximum of 6 cycles. Toxicity was evaluated by NCI-CTC.

**Result:** 30 patients were recruited into the trial. The median age was 45 years (34-65). There were 6 patients who had local recurrent disease, 5 patients had local recurrent plus metastatic disease and 19 patients had metastatic disease. Seven patients were stage IVB at diagnosis. The sites of metastases were 7 in the paraaortic lymph node and supraclavicular lymph node. 6 in the lungs, 5 in paraaortic lymph node, 1 in liver, 4 in supraclavicular lymph node and 1 in subcutaneous nodules. There were 2 complete and 18 partial responses. Overall response rate of 66.6% (20/30) was obtained. Stable disease has been observed in 5 patients (16.7%) and progression in 5 patients (16.7%). There was no chemotherapy related death in this study. One of patients developed pancolitis after the sixth cycle. 9 of patients (30%) developed grade 3 neutropenia. Only grade 1-2 acute and late diarrhea were observed in 20% and 40% respectively. Dose limiting toxicity has been observed in 4 patients (13.3%) with grade 3 renal toxicity. Other non-hematologic and hematologic toxicities did not exceed grade 2 with a median follow up time of 7.5 months. The median time to relapse was 7.4 months. One year disease free survival and overall survival were 11.1% and 66.4% respectively.

**Conclusion:** The preliminary results of this study suggest that the regimen of Irinotecan and cisplatin is feasible and clinical active. However, they produced a short time to relapse like other regimens for metastatic and/or recurrent cervical cancer.