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.

1214 POSTER

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.