1223 POSTER

Prognostic value of Squamous Cell Carcinoma Antigen (SCC) in locally advanced carcinomas of the uterine cervix treated with concomitant chemo-radiotherapy (CCRT) with or without surgery

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Rationale: To evaluate the prognostic value for survival of SCC for pts treated first with an CCRT.

Population: 52 pts treated between 1990 and 1998 by a CCRT; Median age: 53 yrs; Stages: IB: 14%; II: 46%; IIIB-IV: 30%. Nodal involvement on CT Scan: 8 pts.

Treatment: Chemoth.: 5FU: 1 gr/m2 d1-d3 and d21 tod23, in continuous infusion; Cisplatine: 50 mg/m2 d1,d2,d21,d22. Radiotherapy: Pelvic irradiation: 40 Gy in 20 fractions over 5 weeks (split-course of one week).Then reevaluation and surgery (36 pts) or one more cycle of CCRT.

Results: Major clinical response: 45%; Minor clinical regression: 31%. After surgery, complete histological respons: 33%; major histological regression: 36%. Median survival: 63 mths; 2-yr and 5 yr-survivals: 78 and 62%. Major prognostic factors for survival: FIGO Stage; Respons to CCRT.

Value of SCC: 80% of the pts had a high level of SCC at the time of diagnosis. SCC level was clearly correlated with histological differentiation ($p= 0.03$), slightly correlated to the cervix volume ($p=0.09$) and not correlated with stage. Initial SCC level was not correlated with overall survival or disease-free survival. However, decrease of SCC level under CCRT was correlated to the histological respons ($p=0.04$) and to survival ($p=0.01$). 23 pts relapsed. In 66% of these cases, SCC level increase; and in 30% of these relapsing cases, the increase of SCC level precede clinical relapse by several months.

Conclusion: SCC level at diagnosis had no prognostic value in itself. However, its decrease during CCRT had a powerful prognostic value for survival. Moreover, in the follow-up of the patients, SCC could precede the clinical relapse by several months.

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Assessment of microsatellite instability and genetic analysis of mismatch repair genes in sporadic endometrial cancer: identification of different subsets of patients and a MLH1 founder mutation in Sardinia

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Background: Frequency of genome-wide microsatellite instability (MSI) has been demonstrated higher in endometrial cancer (EC) than in other common malignancy, mostly due to defective DNA mismatch repair. To further address questions on the role of this molecular pathway in EC, we screened a series of sporadic EC cases from Sardinia, whose population is genetically homogeneous.

Patients and Methods: Paired normal and tumor samples from 157 Sardinian patients with sporadic EC at various stages of disease were screened by PCR-based analysis using microsatellite markers for MSI. Loss of heterozygosity (LOH) at chromosomal regions of the two major mismatch repair genes, MLH1 (3p21.3) and MSH2 (2p21), was assessed using intragenic and flanking polymorphic markers. Immunohistochemistry (IHC) was performed on MSI+ tumor tissues using anti-MLH1/MSH2 antibodies. Mutation screening was performed on DNA from blood samples of EC patients by DHPLC-based analysis and automated nucleotide sequencing.

Results: Microsatellite analysis revealed the existence of at least two subsets of tumors (probably due to different pathogenetic mechanisms): one, negative for MSI, but carrying specific allelic losses within the 10q25-q26 region and suggesting the involvement of putative tumor suppressor gene(s) (as we previously demonstrated; Cancer 89: 1773-1782, 2000); the second, with a MSI+ phenotype (suggesting a defective DNA mismatch repair). The latter group was analyzed for LOH at chromosomes 3p21.3 and 2p21, and expression of MLH1 and MSH2 by IHC. To date, screening for mutations in the subset of EC patients with MSI+ phenotype and absence of MLH1 protein allowed to identify a germline mutation (I219V) with founder effect in North Sardinia. Further analyses should clarify the presence of additional mutation(s) and their role in EC tumorigenesis. Finally, significance of the presence of the MSI+ phenotype as prognostic factor is under evaluation.

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Docetaxel (D) as neoadjuvant chemotherapy (NAC) in patients (pts) with advanced cervical carcinoma (ACC)

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Purpose: The efficacy and toxicity (Tx) of D as NAC in ACC was evaluated in 38 untreated pts with FIGO's stages IIB to IVA. The median age was 44 yrs (25 - 66 yrs). Stages: IIB 22 pts, IIIB 15 pts and IVA 1 pt.

Methods: Treatment consisted of D 100 mg/m2 IV infusion over one hour. Standard premedication with dexamethasone, dephenhydramine and ranitidine was used. Cycles were repeated every three weeks for 3 courses, followed by surgery if feasible or definitive radiotherapy. Both staging and response (R) assessment were performed by a multidisciplinary team. 106 cycles of therapy were administered.

Results: All pts are evaluable for Tx, while 35 are evaluable for R (3 pts refused further treatment after first cycle). Complete R (CR): 1 pt (3%), partial R: 11 pts (31%), for an overall objective response rate of 34%, no change: 16 pts (46%), and progressive disease: 7 pts (20%). Six pts (17%) underwent surgery and pathologic CR was confirmed in one of them. Neither median time to failure nor overall survival were reached yet. The limiting Tx was leukopenia in 25 pts (69%) (G1-G2:14 pts, G3:10 and G4:1). Neutropenia: 28 pts (78%) (G1-G2: 10 pts, G3: 8 and G4: 10). Myalgias: 17 pts (47%) (G1-G2: 15 pts and G3: 2 pts). Emesis: 21 pts (55%) (G1-G2: 19 pts and G3: 2). Alopecia G3: 13 pts (36%); rash cutaneous 26 pts (68%) (G1-G2: 22 pts and G3: 4 pts).There were no hypersensitivity reactions nor fluid-retention syndrome. The received dose intensity was 91% of that projected.

Conclusion: D is an active drug against ACC with moderate Tx. Further evaluation in association with other agents is clearly justified. Supported by Aventis Pharma.

1226 POSTER

Therapeutic outcome in the primary radiotherapy of cervical carcinoma stage I-IV with external radiotherapy and high-dose-rate intracavitary brachytherapy using a single linear source

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Objective: Most analyses on high-dose-rate brachytherapy of cervical carcinoma report about conventional methods derived from low-dose-rate brachytherapy, e.g. using ovoids. The purpose of this study was to evaluate the efficacy of primary radiation therapy with external radiotherapy and high-dose-rate intracavitary brachytherapy using a single linear source for cervical carcinoma stage FIGO I-IV.

Methods: A retrospective analysis was undertaken of 90 patients (FIGO stage IB 11x, II 27x, III 42x and IV 10x) who underwent primary radiation therapy for cervical carcinoma from 1989 to 1998. External beam radiotherapy and brachytherapy was delivered to central doses of less than 63,6 Gy, 63,3 Gy and 66 Gy. The median follow up was 24 months (1-113).

Results: Relapse-free survival and pelvic control rates were as follows: stage IB 89% and 88%, II 70% and 79%, III 19% and 31%, IV 30% and 44%. With central doses of 66 Gy relapses were seen in 24 of 47 patients. With 63,3 Gy 5 of 20 patients and doses less than 63,3 Gy 14 of 21 patients were diagnosed with a relapse. For all stages we found a better 5-year pelvic control rate with brachytherapy than without brachytherapy. A statistically significant difference was seen between the fractionation of 4 times 6 Gy brachtherapy dose in comparison to no brachytherapy (28% vs. 79%, p=0,024). Late grade 3 or 4 toxicity was 5,7%.

Conclusion: The therapeutic outcome of stage I, II and IV is comparable to other studies using a single linear source and to analyses using conventional brachytherapy methods either in low-dose- or high-dose-rate mode. Unfavourable results of stage III disease are probably due to a relative underdosage of large tumors and aggressive tumorbiology.