Vaginal Brachytherapy for High-Intermediate Risk Endometrial Cancers

Data from a randomized phase 3 trial indicate that vaginal brachytherapy (VBT) may be a better option than pelvic radiotherapy for treating high-intermediate risk (age>60 and stage 1C grade 1-2 or stage 1B grade 3; any age and stage 2A grade 1-2 or grade 3 with <50% invasion) endometrial cancers because of a lower rate of side effects, leading to enhanced quality of life.

Remi A. Nout, MD, Leiden University Medical Center, Leiden, The Netherlands, reported the results of the PORTEC-2 trial (NCT00376844), in which patients were randomly assigned to either external beam radiation therapy (EBRT) (214 patients) or VBT (213 patients) as treatment for high-intermediate risk endometrial cancers following total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO). EBRT consisted of 46 Gy that was delivered in 23 fractions; VBT was delivered at a high-dose rate of 21 Gy in 3 fractions or at a low-dose rate of 30 Gy in a single fraction. Vaginal relapse rate was chosen as the primary endpoint, because data from PORTEC-1 indicated that the vagina was the major site of relapse in patients with endometrial cancer who had no further treatment after TAH-BSO (Creutzberg et al. *Lancet* 2000).

Dr. Nout reported that at a median follow-up of 36 months, the vaginal relapse rates were not significantly different between the 2 arms (0.9% for VBT vs 1.9% for EBRT; p=0.97). The rate of pelvic recurrence was higher for patients in the VBT arm (3.5% vs 0.6%; p=0.03), but Dr. Nout pointed out that the majority of those pelvic recurrences was associated with distant recurrence. Both overall survival and relapse-free survival rates were similar for both arms of the study. The 3-year disease-free survival rate was 89.7% for VBT compared with 88.6% for EBRT (p=0.68). The overall survival at 3 years was 90.8% for VBT and 90.3% for EBRT (p=0.96).

While the efficacy of the 2 treatments was similar, VBT offered an advantage in terms of quality of life, said Dr. Nout. He noted that patients who received VBT after surgery reported significantly less diarrhea (moderate to severe: 6% vs 22%; p<0.001), which resulted in significantly fewer limitations in daily activities (p<0.001) and significantly better social functioning (p<0.002).

In addition to improved quality of life, VBT offers the benefit of a lower time commitment for treatment. Patients who receive 23 fractions of EBRT usually receive treatment 5 times per week for approximately 5 weeks. In contrast, treatment with VBT is usually given with high-dose rate brachytherapy, which requires three outpatient visits in a two week period.

"Vaginal brachytherapy is safe and effective for patients with high-intermediate risk features," said Dr. Nout, in conclusion. "[It] should be the treatment of choice for patients with high-intermediate risk endometrial carcinoma."

Evaluation of Doublet Chemotherapy Regimens for Advanced Cervical Cancer

The results of several Gynecologic Oncology Group (GOG) trials have established doublet chemotherapy with standard-dose cisplatin and paclitaxel as the preferred treatment for advanced or recurrent cervical cancer. The GOG 204 trial (NCT00064077) was conducted to evaluate 3 experimental cisplatin-containing doublet chemotherapy regimens against the standard of cisplatin and paclitaxel. The findings indicated that none of the doublet regimens was superior to cisplatin plus paclitaxel in terms of response rate, progression-free survival (PFS), or overall survival (OS).

The experimental arms in the phase 3 trial consisted of chemotherapy with cisplatin in combination with vinorelbine, topotecan, or gemcitabine. Bradley J. Monk, MD, University of California, Irvine, CA, presenting on behalf of the GOG investigators, noted that the study began as a 2-arm trial that was designed to compare cisplatin and vinorelbine against cisplatin and paclitaxel. The other arms of the trial were added when other studies suggested benefit of topotecan and gemcitabine. The trial was stopped prematurely in April 2007 after a planned interim futility analysis indicated that the 3 experimental arms were not likely to be superior to the standard arm by the end of the study, said Dr. Monk. At the time that the study was closed, 513 of a planned 600 patients had enrolled. Data on response and survival were available for 434 patients. The primary endpoint was OS.

OS was not significantly better for any of the experimental doublet regimens, with the relative hazard ratios (HRs) for all 3 regimens favoring cisplatin and paclitaxel (Table 1). Similarly, the HRs favored cisplatin plus paclitaxel with respect to PFS (a secondary endpoint). Dr. Monk reported that the median PFS for cisplatin plus paclitaxel was 12.9 months, compared with 10 to 10.3 months for the 3 other doublet regimens.

Table 1. Hazard Ratios for the 3 Experimental Doublet Regimens Relative to the Reference Arm of Cisplatin Plus Paclitaxel.

	Cisplatin + Gemcitabine	Cisplatin + Topotecan	Cisplatin + Vinorelbine
OS	1.322	1.255	1.147
PFS	1.394	1.268	1.357

The overall objective response rate (complete plus partial) according to RECIST criteria was 25%. The response rate was highest for cisplatin plus paclitaxel (29.1%) and lowest for cisplatin plus gemcitabine (22.3%). "This difference was not statistically significant but might be clinically important," said Dr. Monk. The rate was 25.9% for cisplatin plus vinorelbine and 23.4% for cisplatin plus topotecan.

Dr. Monk noted that the toxicities of the regimens were similar, except for a lower frequency of leukopenia and neutropenia in the cisplatin plus gemcitabine arm and a higher frequency of alopecia in the cisplatin plus paclitaxel arm.

Adjuvant Gemcitabine Extends Overall Survival in Patients with Resected Pancreatic Cancer

If their disease is caught early enough, patients with pancreatic cancer (PC) may undergo a resection of the diseased organ; this procedure, though intended to be curative, most often results in only a modest increase in overall survival (OS). As with other cancers, it is possible that adjuvant chemotherapy may improve long-term outcome, but there is no approved or accepted therapeutic in this setting. For patients with advanced PC, treatment with gemcitabine (GEM) is the standard of care, making it the logical choice for investigative use after resection of the pancreas.

To date, there has not been enough evidence to warrant the standardization of this approach. However, data presented by Ulf Neumann, MD, Charité Universitatsmedizin Berlin, Berlin, Germany, added to the position that adjuvant treatment with gemcitabine should be seriously considered (Abstract #LBA 4504. ASCO 2008).

This phase 3, randomized, multicenter investigation (CONKO-001) looked at the adjuvant use of gemcitabine versus observation in patients with complete PC resection (R0 or R1; n=368). Patients were first stratified by resection status, nodal tumor involvement, and tumor stage and then randomized to observation or treatment with GEM 1000 mg/m2 on Days 1, 8, and 15 every 4 weeks for a total of 6 months. The primary endpoint of the study was disease-free survival (DFS) with secondary endpoints that included OS and the parameters of toxicity.

"We already demonstrated safety data and efficacy for adjuvant treatment with gemcitabine in patients with resected pancreatic cancer 3 years ago," (Abstract #4014. ASCO 2007; Oettle et al. *JAMA* 2007) said Dr. Neumann. This final analysis, performed in March, incorporated data up to December 1, 2007, with 303 events in DFS (86.6%) and 293 events for OS (82.8%).

Results showed a median DFS of 13.4 months for GEM versus 6.9 months for observation (p=0.001). The proportion of patients with DFS at 5 years was 16% for GEM versus 6.5% for the observation arm. "Additionally, an unplanned subpopulation analysis showed the beneficial effect of gemcitabine in R0, R1, node-positive, node-negative, T1-2, and T3-4 tumors... all significant."

Perhaps what was most interesting was the significant improvement of OS in the final analysis, which in the preliminary report of this investigation had not reached significance. In this final analysis, median OS was 22.8 months for GEM as compared with 20.2 months for observation (p=0.005). This benefit was maintained out to 5 years, at which point a survival rate of 21% was recorded for the treatment arm versus 9% for observation.

Sequential Therapy with Gefitinib for Advanced Non-Small Cell Lung Cancer

In previous studies, gefitinib combined with chemotherapy has provided no survival gain compared with chemotherapy alone for patients with advanced non-small cell lung cancer (NSCLC). However, a phase 3 trial has shown that sequential therapy with gefitinib may offer clinical benefit after platinum-based doublet chemotherapy in this setting.

The West Japan Thoracic Oncology Group trial (WJTOG 0203) (NCT00144066) involved patients who were randomly assigned to 3-6 cycles of chemotherapy alone (298 patients) or to 3 cycles of chemotherapy followed by daily gefitinib until disease progression (300 patients). The chemotherapy regimens consisted of cisplatin or carboplatin in combination with irinotecan, docetaxel,