Supplementary Data 1. A randomized phase III trial comparing concurrent chemoradiation therapy (CCRT) versus CCRT followed by adjuvant chemotherapy in locally advanced cervical cancer

INTERVENTIONS

1. Radiation therapy

Radiation therapy started within 30 days after randomization.

1) External beam pelvic radiation therapy

Radiation was administered using a standard 2-field (AP-PA) or 4-field box techniques (AP-PA-RL-LL) with 6–10MV photon. In brief, 45–50.4 Gy of radiation was given in 25–28 fractions: 1.8–2 Gy/day, 5 days a week. The superior border was at the L4–L5 interspace and the inferior border covering the obturator foramen or 2–3 cm below the gross tumor. The lateral borders included the pelvic nodes 1.5–2 cm beyond the bony pelvic walls. The anterior border was 3 cm anterior to the anterior margin of L5 and the posterior border was to the S2–3 interspace. Central shielding and parametrium boost were considered at the discretion of the physician.

If the absolute neutrophil count (ANC) was <1,000/mm³ and platelets were 50,000/mm³, external radiation therapy was delayed for 1 week. If radiation therapy was delayed, chemotherapy was withheld. Radiation therapy was also postponed for patients who developed local toxicity of radiation dermatitis, proctitis, dysuria, or vaginitis ≥ grade 3 until improvement. Any patient who could not restart radiotherapy within 3 weeks was removed from the study.

2) Intracavitary brachytherapy (ICBT)

The patients had high-dose rate ICBT 6.0-7.5 Gy for 3-4 fractions. To begin brachytherapy, patients must have had ANC >1000/dL, platelets >50,000/dL, and non-hematological toxicity ≤ grade 2. For patients requiring a longer time to recover from toxicity, up to 5 weeks of rest between the end of external radiotherapy and the beginning of brachytherapy was allowed or else the patient would be discontinued from the study.

2. Chemotherapy
1) Concurrent chemoradiation

During the period of radiation therapy, all patients received cisplatin 40 mg/m² intravenous (IV) over 60 minutes once weekly or 7 days apart for 6 weeks. Cisplatin administration in that particular week was withheld with any events of toxicity.

2) Adjuvant chemotherapy

Paclitaxel and carboplatin was administered IV every 4 weeks for 3 cycles starting on day 28 after the completion of CCRT for 3 cycles. Paclitaxel 175 mg/m² in 500 mL of normal saline solution using non-polyvinyl chloride equipment with in-line filtering was administered intravenously over 3 hours. Pre-medication drugs of dexamethasone, diphenhydramine and ranitidine were given prior to paclitaxel infusion. The carboplatin dose was calculated by the Calvert formula given at area under the curve 5. Dose adjustment was allowed in any event of toxicity. A 45-day delay was allowed after CCRT and between each cycle of chemotherapy.
CLINICAL OUTCOMES ASSESSMENT

All assessments were performed by the principal investigators in each participating hospital. The clinical outcomes were recorded and verified by the principal investigators in each participating hospital, the data manager of the Data Management Unit, the major principal investigator and the Data Safety Monitoring Board.

1. Assessments

1) At baseline

At baseline, all patients underwent clinical staging by complete physical examination including vaginal and rectal examination, chest x-ray, whole abdominal computed tomography, and laboratory tests including complete blood count (CBC), blood urea nitrogen (BUN), creatinine (Cr), Cr clearance, electrolytes, liver function test, and anti-human immunodeficiency viruses serology.

2) During treatment

During concurrent chemoradiation treatment, all patients had a weekly physical examination, CBC, BUN and Cr. The same approach was performed on day one of each adjuvant chemotherapy (ACT) cycle with an addition of LFT and electrolytes for the patients in arm B.

3) After treatment

The patients were followed for a status of tumor each month after completion of CCRT for 4 months and were then followed according to the standard practice: every 3–4 months for 24 months and every 6 months for 12 months. The surveillance according to the trial continued unless there were persistent diseases, progression, or recurrence requiring salvage treatment. During the surveillance, whole abdominal computed tomography scan and chest-X ray were planned every 6 months for 2 years and yearly respectively or whenever clinically indicated.

2. Clinical outcomes

Progression-free survival (PFS) was calculated from the date of treatment initiation until the date of disease persistence, progression or recurrence. Data were censored on the date of the last follow-up in the patients who had no progression, date of death due to other causes, or date of treatment discontinuation for toxicity or other
causes. Overall survival (OS) was obtained from the date of treatment initiation to date of death from cancer or any relevant causes or last evaluation in patients who were alive at the end of the study.

The response defined by the Response Evaluation Criteria in Solid Tumors 1.1 criteria was concluded at approximately 4 months after CCRT in arm A or 1 month after the last ACT in arm B, or earlier when an event of disease progression occurred. Complete response was defined as disappearance of disease whereas persistence was defined as presence of any size of tumor at the time of assessment. An increase in the size of existing lesion or an appearance of new lesions was determined as progressive disease. Recurrence was defined with any evidence of disease after complete response and was defined as loco-regional or systemic.

Adverse events were graded and categorized by the Common Toxicity Criteria V. 4.0.
INTERIM ANALYSIS

1. Interim analysis for safety

Data of the first 20 patients (approximately 10 in each arm) and every 50 subsequent patients were analyzed for safety after their treatments were completed. Data were reported to the Data Safety Monitoring Board when there were toxicities ≥ grades 3. Discontinuation of the trial was planned at any time point if more than 5% deaths of the enrolled patients were encountered.

2. Interim analysis for efficacy or futility

Clinical outcomes were analyzed when approximately half or 250 of the patients were recruited into the study. The proposal of the trial was that the ACT should increase the PFS of at least 15% to be clinically significant. If the interim analysis demonstrated a clear benefit of ACT defined as 30% PFS improvement or double of the expected benefit, we would terminate the trial prior to the completion. On the contrary, if the interim analysis could not demonstrate a 10% increase of PFS and the statistical estimation that the probability or the conditional power when the study ended would not be sufficient, we would terminate the study prior to the completion. Bootstrap analysis would be conducted in any circumstance of study discontinuation.
RESULTS

1. Non-compliance

We found number of patients did not have treatment as planned either in the CCRT or ACT phase or both. The reasons for having no or incomplete CCRT or ACT of 51 patients are shown in Supplementary Table 1.

2. Response

Data of 259 patients (129 in arm A and 130 in arm B) were included in the interim analysis. All 13 patients who did not complete CCRT and had persistent diseases were regarded as failure of treatment. The tumor statuses, which were evaluated in a longitudinal timelines, tended to improve during consecutive months of evaluation from the first to fourth month after CCRT in both arms. Significantly better improvement of tumor shrinkage was demonstrated in arm A than in arm B at the first to the third evaluation except at the fourth evaluation when the difference was not significantly different (Supplementary Table 2).

3. Failure of treatment

With a median follow-up of 27.4 months (range, 3.2–49.0 months), 34 patients (13.1%) who had complete response experienced recurrences: 20 patients (15.5%) in arm A and 14 (10.8%) in arm B (p=0.123). The sites of recurrences were loco-regional in 8 patients, systemic in 20, and combined loco-regional and systemic in the other 6. The corresponding rates of recurrences in arm A and arm B were 4.0% both for loco-regional (p=0.871), 10.1% vs 5.4% for systemic (p=0.029), and 2.3% both for combined loco-regional with systemic (p=0.910). The response rates, failure of treatment and sites of failure are shown in Table 3. A median time to events (progression or recurrence) among 81 patients was 6.9 months (range, 0.2–31.6 months): 8.2 months (range, 0.2–31.6 months) in arm A and 6.4 months (range, 0.3–26.4 months) in arm B. Median PFS was 18.7 (range, 0.2–49.0 months); 20.0 months (range, 0.2–49.0 months) in arm A and 17.6 months (range, 0.3–46.9 months) in arm B. The 3-year PFS was 64.9% (95% CI=58.5%–71.4%); 66.6% (95% CI=57.4%–75.8%) in arm A and 63.4% (95% CI=54.6%–72.2%) in arm B (Fig. 2). The hazard ratio (HR) for PFS of arm B compared to arm A was 1.26 (95% CI=0.82–1.96%; p=0.293).

4. Death

Overall, 50 deaths (19.3%) were encountered: 21 (16.3%) in arm A and 29 (22.3%) in arm B (p=0.219). Among these, 43 deaths were determined to be from disease (16 in arm A and 27 in arm B) and 2 deaths (arm A) were
possibly related to study treatment (diarrhea or sepsis). The other 5 deaths (3 in arm A and 2 in arm B) were not relevant to cancer or its treatment. Unrelated deaths were censored for OS analysis. The median OS of all patients was 27.4 months (range, 3.2–49.0 months): 20.2 months (range, 0.2–49.0 months) in arm A and 17.6 months (range, 0.3–46.9 months) in arm B (p=0.233). The 3-year OS was 74.9% (95% CI=68.2%–81.5%): 80.1% (95% CI=71.9%–88.3%) in arm A and 69.5% (95% CI=59.3%–79.7%) in arm B (Fig. 3). The HR for OS of arm B compared to arm A was 1.42 (95% CI=0.81–2.49; p=0.221).

5. Outcomes per protocol analysis

After excluding 51 patients who did not have treatment as planned (13 in both arms who did not complete radiation treatment, 1 patient in arm A who had ACT, and 37 patients in arm B who did not have or had incomplete the 3 cycles of ACT), the data of 208 patients (123 in arm A and 85 arm B) were analyzed per protocol. Response rates at 4 months, recurrence and deaths were not significantly different between the 2 groups are shown in Supplementary Table 3.