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Beyond Platinum for Metastatic and Recurrent Carcinoma of the Cervix

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In this issue of Onkologie Takano et al. [1] report complete remissions in two patients with metastatic and recurrent cervical cancer. Prior to recurrence, one patient had received chemoradiation for locally advanced disease, and the other had been treated with adjuvant pelvic radiation following hysterectomy. Importantly, both of these patients were treated with weekly paclitaxel (80 mg/m^2) plus carboplatin (AUC 2.0) (days 1, 8, 15) and weekly bevacizumab (days 1, 8, 15, 21). Case reports rarely warrant editorials, but these are noteworthy because the activity and tolerability of the antivascular agent bevacizumab in combination with cytotoxic therapy for metastatic and recurrent cervical cancer is the subject of the ongoing phase III, randomized trial of the Gynecologic Oncology Group (GOG 240) [2].

The landscape has changed over the years. Due to successful screening programs with Papanicoloau testing (with and without high-risk HPV triage/co-primary screening in women over 30), incidence and mortality rates of cervical cancer in the United States and Western European nations have dramatically decreased. In addition, concurrent platinum-based chemoradiation has become the standard of care for locally advanced disease [3]. Many recurrent tumors may therefore be platinum resistant.

The GOG has completed no fewer than 8 multi-center phase III randomized trials to study platinum-based therapies for recurrent and/or metastatic disease [4, 5]. The most recently completed study, GOG 204, compared 4 platinum-based doublets using paclitaxel, topotecan, gemcitabine, and vinorelbine [6]. None of the experimental arms out-performed the reference arm. For this reason, cisplatin plus paclitaxel has been selected as the control arm for GOG 240 which was activated in April 2009 and is one of 3 ongoing phase III trials being conducted throughout the world for this patient population. The Japan Clinical Oncology Group (JCOG) is currently enrolling patients onto a trial comparing cisplatin plus paclitaxel vs. carboplatin plus paclitaxel (fig. 1) [7]. The non-platinum doublet, topotecan plus paclitaxel is being studied by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) (fig. 2) [8].

In GOG 240, the experimental arms have been designed to answer two critical questions. The first is a chemotherapy question and whether the non-platinum doublet topotecan plus paclitaxel would have greater activity in the recurrent setting given the increased usage of platinum-based chemoradiation upfront for locally advanced cancers. For these two case reports, the inclusion of biologics by Takano's team was a brilliant stroke. Importantly, the second question to be addressed by GOG 240 is whether targeted therapy has a role in this population.

Signal transduction pathways governed by the epidermal growth factor receptor (EGFR) and those involved in angiogenesis have been the subject of recent investigations. At ASCO 2009, Movva et al. [9] have reported on EGFR immunostaining in 80 patients with cervical cancer. Although the investigators did not detect any correlations between EGFR expression and clinical parameters (including overall survival (OS)), EGFR inhibitors of the extracellular domain (e.g. cetuximab) may be expected to be useful for the treatment of cervical cancers that overexpress this receptor. Randall et al. [10] have recently shown that tumor angiogenesis as measured by CD31 microvessel density is an independent prognostic factor for both progression free survival (PFS) and OS in high-risk, early-stage cervical cancer. In the setting of metastatic and/or recurrent disease, Monk et al. [11] conducted a randomized phase II study comparing the oral tyrosine kinase inhibitors pazopanib and lapatinib. Pazopanib is anti-angiogenic and targets the vascular endothelial growth factor (VEGF) and the platelet-derived growth factor receptors, while lapatinib targets EGFR and HER2. In this study of 235 patients, both PFS and OS were significantly prolonged with the anti-vascular agent pazopanib compared to lapatinib.

A small case series by Wright et al. [12] described the successful combination of bevacizumab with cytotoxic agents in the recurrent and metastatic setting among previously irradiated patients. Importantly, the antiangiogenesis agent bevacizumab in combination with chemotherapy has been FDA-approved for locally advanced and recurrent breast cancer,

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first and second line therapy for metastatic colorectal cancer, untreated non-small cell lung cancer (NSCLC), and glioblastoma multiforme. The drug is currently being studied by the GOG in primary advanced and platinum-sensitive recurrent ovarian carcinoma, as well as in uterine endometrial cancers and carcinosarcomas. A phase II evaluation of bevacizumab at 15 mg/kg q21 days was undertaken within the GOG (protocol 227C) [13]. The 26% risk reduction (RR) of bevacizumab among previously irradiated patients was among the highest RRs noted within the GOG's phase II experience for recurrent cervical cancer, and the prolongation in PFS was also impressive. These data strongly support the addition of bevacizumab to the therapeutic regimens employed in the two patients reported by Takano et al. [1].

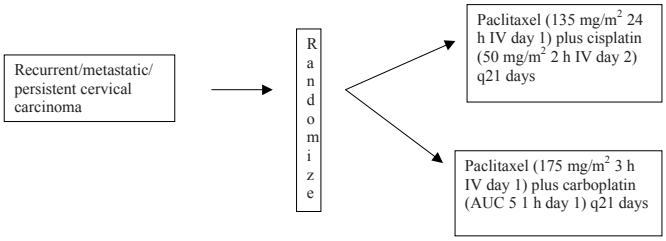

Fig. 1. Phase III clinical trial design of JCOG protocol 0505.

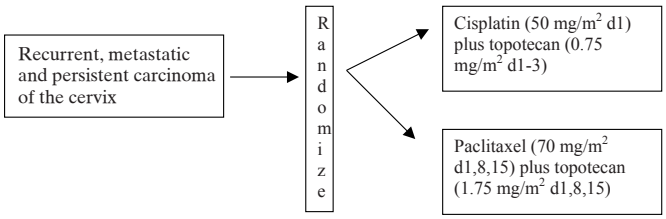

Fig. 2. Phase III clinical trial design of AGO protocol IFG-01-0106.

Given the potential shared tumor biology between NSCLC and cervical cancer along with the activity of platinum plus paclitaxel with bevacizumab in NSCLC [14], a platinum-based regimen which includes bevacizumab was selected to be one of the experimental arms in GOG 240. Assuming no interaction between the non-platinum doublet and bevacizumab, a 2×2 factorial design has been selected to answer both the chemotherapy question and the biologic/antivascular question. The schema for GOG 240 appears in figure 3.

Perhaps a second important contribution of Takano's paper is that we are seeing increasing evidence that therapy for metastatic cervical carcinoma does not need to be solely palliative. In 2007, Qui et al. [15] reported on long-term survivors who presented with supraclavicular metastases. Although both patients in the present report have not had extended follow-up, it is nonetheless exciting that both had been treated with measureable disease and experienced complete responses to cytoxotic and antivascular therapy. Notwithstanding significant unanticipated toxicities, the ongoing trials of the AGO, JCOG, and GOG have been positioned to further refine therapeutic options for this disease.

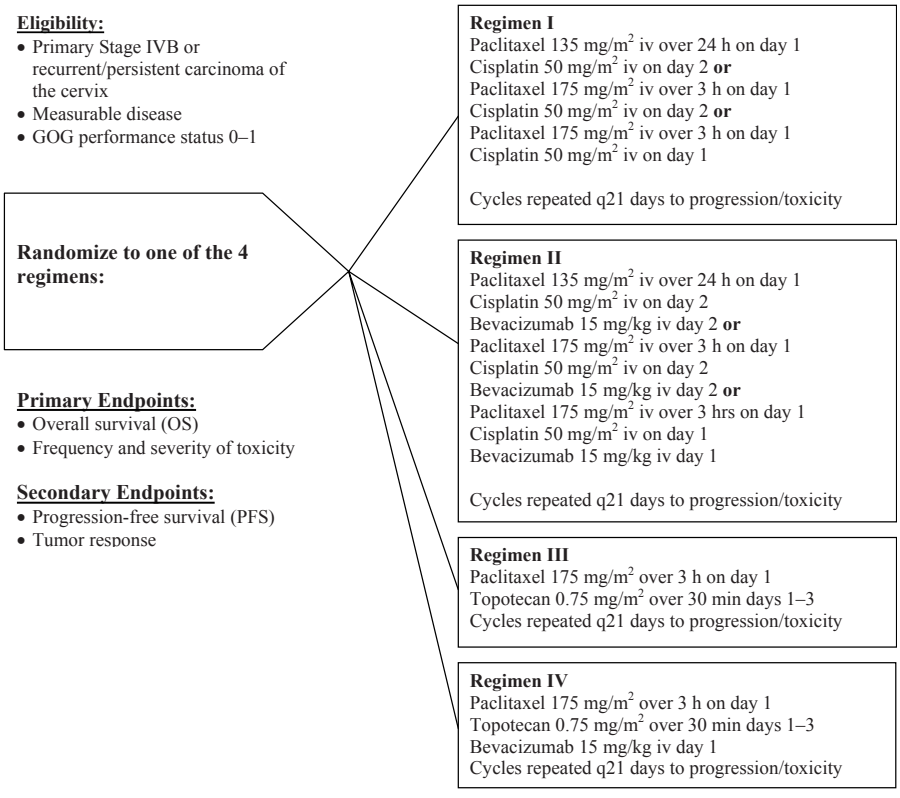

Fig. 3. Phase III trial design of GOG protocol 240.

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