Gynecologic Oncology Reports 42 (2022) 101045

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

One small step can lead to one giant leap

Treating exceedingly rare tumors can be both a terrifying and a liberating experience. With an incidence of 0.06 cases per 100,000 women each year, high grade neuroendocrine cervical cancer can certainly be considered an ultrarare malignancy (Chen et al., 2008). Although treatment algorithms for women with newly diagnosed high grade neuroendocrine cervical cancer have been proposed, standard of care therapeutic regimens for recurrent disease have not been established. In fact, published guidelines form the Society of Gynecologic Oncology (SGO), the Gynecologic Cancer InterGroup (GCIG), and the National Comprehensive Cancer Network (NCCN) are conspicuously lacking in strong recommendations for recurrent disease (Salvo et al., 2019). In effect, they each say "Recurrent disease? You're on your own." When little is known about a tumor and options are limited, oncologists are afforded some leniency in what they prescribe to their patients. As prospective clinical trials are sparse in the rarest gynecologic malignancies, clinicians with no standard of care options may adopt regimens from tumors with similar histologies at other sites, apply targeted therapies based on molecular testing, or turn to small cases series for "inspiration". These pioneers need just be thoughtful and creative.

For example, in 2013 we started giving patients with recurrent high grade neuroendocrine cervical cancer the three-drug regimen topotecan, paclitaxel, and bevacizumab. At initial glance, this combination may seem somewhat arbitrary, but in reality we had what we believed to be sound rationale (Frumovitz et al., 2017). First, topotecan and paclitaxel were known to have activity as single agents in patients with small cell lung cancer – a tumor type that histologically appears quite similar to small cell cervical cancer which was the subtype found in 80% of high grade neuroendocrine cervical cancer patients. Second, small cell cervical cancer tumors expressed the VEGF receptor on immunohistochemistry staining in almost 95% of cases. Next, most patients with recurrent high grade neuroendocrine cervical cancer likely would have had primary therapies similar to women with recurrent adenocarcinoma, squamous, or adenosqaumous cervical carcinoma namely combinations of surgery, radiation, and/or chemotherapy. The latter patients were given this same regimen in one of the four arms of GOG-240 and had tolerated the combination with acceptable toxicities. Finally, all three drugs (topotecan, paclitaxel, and bevacizumab) were FDA approved and compendium listed for the treatment of recurrent cervical cancer (any histology) so we knew insurers would likely reimburse. Ultimately a small retrospective study showed that when compared to women who did not receive topotecan, paclitaxel, and bevacizumab, patients who did had a significantly longer progression free survival and more women remained on treatment at 12- and 24-months (Frumovitz et al., 2017). Although this series only had 13 patients who received the three-drug regimen, due to lack of other options many other centers have adopted it as part of their armamentarium for treating women with recurrent disease (Stelwagen et al., 2021; Winer et al., 2021; Harris et al., 2009). Essentially a small case series of 13 patients was able to establish a standard of care option.

Might we now have another option for women with this deadly disease? In this issue of *Gynecologic Oncology Reports*, Towner et al. report on 3 women with recurrent high grade neuroendocrine cervical cancer who received the immunotherapy combination of ipilimumab and nivolumab. All three women had a clinical benefit with two patients progressing only after one year on treatment and a third who continues on the combination at 83 weeks. In a disease whose median overall survival after recurrence is <1 year, the reported outcomes are truly remarkable. These 3 patients benefitted incredibly from their oncologists' creativity. These authors should be congratulated for their vision in applying this regimen to women with recurrent high grade neuroendocrine cervical cancer.

The author's "inspiration" for prescribing combination ipilimumab and nivolumab to these women came from multiple sources. First, the combination has been shown to have a response rate of 20% in patients with small cell lung cancer (Antonia et al., 2016). Second, a basket trial of patients with non-pancreatic neuroendocrine reported an overall response rate of 44% in those patients with high grade malignancies and this included 3 patients with high grade neuroendocrine cervical cancer, 1 of whom also had a response (Patel et al., 2020). Finally, there was also a single case report of a complete response to ipilimumab and nivolumab in a woman with recurrent high grade neuroendocrine cervical cancer (Paterniti et al., 2021). Together, these publications formed a sound rationale for a treatment attempt with this immunotherapy combination in women with essentially no other options.

This case series reports a benefit rate of 100% yet we know that due to publication bias there are almost certainly others around the world who have received this regimen without benefit. Ideally this early signal would be confirmed in a formal, prospective trial. However, clinical trials in ultrarare cancers are exceeding difficult to complete due to slow accrual and funding sources (collaborative groups, industry, NIH/NCI) are often wary to support. That said, there currently is an ongoing trial with cadonilimab (AK104), a bispecific PD-1/CTLA-4 antibody, for women with recurrent high grade neuroendocrine cervical cancers (NCT05063916) so we can occasionally get prospective studies approved and open. Short of a clinical trial for ipilimumab and nivolumab, though, we would encourage pooling of cases into registries so that we can get more complete data on all patients who receive the regimen. For, as demonstrated by our experience with topotecan, paclitaxel, and bevacizumab, even small case series can change the standard of care in ultrarare cancers. Based on this and other reports, as well as the lack of

https://doi.org/10.1016/j.gore.2022.101045

Available online 13 July 2022

other active therapies in women with this terrible disease, we would strongly encourage providers to consider the combination of ipilimumab and nivolumab as an option in patients with recurrent high grade neuroendocrine cervical cancer.

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