Focused Review

What Is the Appropriate Approach to Treating Women With Incurable Cervical Cancer?

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Abstract

Women should not die of cervical cancer…but they do. Most cases of cervical cancer are preventable and, if caught early, highly curable. Despite this, cervical cancer is the second most common cause of cancer death in women worldwide. Unfortunately, cure is less likely when the disease is diagnosed at an advanced stage. Treatment of locally advanced disease often has serious lifelong side effects, including cystitis, proctitis, intestinal strictures, fistulas, vaginal agglutination/sexual dysfunction, and chronic pain. Unresectable recurrent disease may be associated with all these symptoms, in addition to disturbing malodorous discharge and bleeding and a life expectancy of less than 6 to 10 months. Supportive/palliative care interventions are needed at diagnosis and recurrence. Honest, conflict-free conversations about potential for response and expectations are needed for women with recurrent disease to help preserve and improve quality of life and avoid treatments that offer no benefit. Aims of trial design should include not only molecular targeting but also supportive care objectives, such as reducing pain, anxiety, depression, cachexia, and fatigue. A β-adrenergic blockade could potentially be part of these intervention trials. This article addresses the following questions and issues: whether therapeutic treatment of incurable cervical cancer is ever appropriate, the common symptoms of recurrent cervical cancer, the quantifying benefits of treatment, decision aids in treatment planning, doctor-patient candor, and integrating psychosocial factors into treatment. (*JNCCN* 2013;11:348–355)

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Case Study

MS is a 54-year-old woman with biopsy-proven recurrent cervical cancer in the previously irradiated pelvic field, who presented for a second opinion. She had no measurable disease according to CT or MRI, and had bilateral percutaneous nephrostomy (PCN) tubes. At this first encounter, the author was to consider the pros and cons of surgical, cytotoxic, or targeted treatment, although the cancer was suspected to be incurable.

The patient indicated that her primary concerns related to wetness (although improved with PCNs) and a malodorous vaginal discharge. Superseding these distressing symptoms was chronic pain with both somatic and neurologic components.

She refused a physical examination because of pain but agreed to undergo examination under anesthesia. A palpable rind of necrotic tissue and tumor (biopsy-proven) covered the circumference of her vagina; it was continuous with a gaping vesicovaginal fistula and inseparable from her pelvic side wall. As is often the situation, her CT was not able to represent the extent of disease because of the infiltrative nature of the tumor in irradiated tissue.

Her disease was not surgically resectable and thus she was not an exenteration candidate. Potential treatments were discussed. With sensitivity, the author told the patient that her cancer was incurable. Her options might have included a clinical trial had her tumor been "measurable" by radiologic image. Thus, the only remaining therapeutic option was chemotherapy. The term *therapeutic* was clearly described as having no chance of cure and offering at most a limited-duration response. The author also emphasized that this therapy would most likely make her feel more tired and potentially more nauseated, and had the possibility of increasing the risk of a serious infection. The alternative option discussed was to receive no "therapy" and instead focus on relieving symptoms with active supportive care (which she would receive either way) and eventually hospice. MS

was not interested in this latter option; "I'm a fighter, I'm going to fight this 'til the end" she said. For the next few weeks, the author and patient focused on achieving improved pain control, better bowel movements, and decreased wetness and discharge.

Despite the author's concerns about side effects and inability to measure response, the patient desired chemotherapy off-trial. They discussed the options, specifically either paclitaxel and carboplatin (29% response rate [RR]) or cisplatinum and topotecan (23% RR), and the contrasting side effects.[1] The patient chose paclitaxel and carboplatin because of her limited transportation options, and the author and patient charted a plan to obtain imaging every 3 to 4 cycles to monitor for progression.

MS received paclitaxel and carboplatin for 9 months with no evidence of progression (or response) until she developed a rectovaginal fistula. During those 9 months she had some intermittent admissions for early pyelonephritis, exchange of PCN tubes, and antibiotics, but most importantly she experienced no neuropathy nor worsening quality of life (QOL). After a laparoscopic diverting colostomy, the author recommended a break from chemotherapy; within a few weeks the patient developed worsening back pain, which was shown to be caused by a vertebral metastasis. She received palliative radiation and the author discussed a recommendation for hospice. The patient expressed her disagreement and desire to continue with chemotherapy, but with time and lack of improvement in performance status, the author was able to help MS accept the shifting goals and redirection of "hope".

Background

Cervical cancer is uniquely situated to be eradicated with existing medical tools. Despite human papillomavirus vaccines, cervical cancer will remain a serious health threat for at least 50 years, especially while the ability to fully vaccinate women against it is limited by politicization of the vaccination mandate, lack of access to care, and low medical literacy. Lack of access to care correlates with delay in diagnosis and advanced stage at presentation, and may curtail survival. Most cases of cervical cancer are not only preventable but, if caught early, curable. Despite this, cervical cancer is the second most common cause of cancer death in women worldwide.[2]

Much of the expense related to treating cervical cancer is for therapy with curative intent, but a sizeable portion is spent on palliation of treatment-related side effects in advanced disease, therapies with no proven benefit (not to mention enormous costs), and supportive care during clinically challenging situations. Knowing that barriers to medical care and limited social support result in poor rates of screening and delayed treatment, it should come as no surprise that these same obstacles prevent women from receiving state-of-the-art supportive care.

Treatment of locally advanced disease with radiation often has serious lifelong side effects, including cystitis, proctitis, intestinal strictures, fistulas, vaginal agglutination/sexual dysfunction, and chronic pain. Unresectable recurrent disease may be associated with all of these symptoms, along with disturbing malodorous discharge and bleeding, and is associated with a life expectancy less than 10 months. Supportive/palliative care interventions are needed at diagnosis and recurrence. Honest, conflict-free conversations about potential for response and expectations are needed for women with recurrent disease to avoid treatments that have no benefit to help preserve and improve QOL.

Is Therapeutic Treatment of Incurable Cervical Cancer Ever Appropriate?

Chemotherapy for recurrent, unresectable cervical cancer in a previously irradiated field is always palliative. The complexity of decisions for palliative treatment lies both in the beliefs and presentation of the situation by the physician and the hopes and beliefs of the patient. Unfortunately, as many as 20% of patients with cancer receive chemotherapy within 2 weeks of death and many die in an acute care bed.[3,4] One reason for this is that physicians overestimate survival to themselves and further overestimate the survival they present to patients.[5] Furthermore, doctors, knowingly or unknowingly, influence patients' decisions about their medical care.[6,7] That said, patients are willing to undergo treatments that offer very little chance of any clinical benefit (but major risk of toxic effects) because of hope, a dearth of concrete information, and lack of treatment decision aids. Patients with young children who have cervical cancer may do "everything" to "fight 'til the end" and "never give up."[8]

And, even though patients want their doctors to be truthful, doctors may find it difficult to be totally honest because they empathize and try to soften the blow to the patient (and in effect to themselves).[9,10]

Regardless of whether they enter a clinical treatment trial or receive chemotherapy off-trial, women with recurrent cervical cancer who receive a second- or third-line regimen have an average survival of 6 to 8 months.[11] Chemotherapy RRs are regrettably low for several reasons, including scarring and hypoxia in irradiated tissue. Furthermore, women who have received radiation often have limited bone marrow function. Finally, radioresistance is often correlated with chemoresistance.[12] Knowing this, physicians must ask themselves if these therapies have essentially no chance of improving survival and most likely no chance of improving QOL, then why do they continue to be administered? Possible explanations are that writing a "chemotherapy prescription" may be easier than facing the realities of these tragic situations, or that physicians themselves promote false hope due to a known propensity to overestimate survival. Conflicts of interest related to benefits associated with enrolling patients on clinical trials are, hopefully, less likely. More likely, the physician's willingness to treat originates from a deep desire to help with a dearth of effective tools to do so.

Truthfully, very few circumstances exist in which a woman with recurrent and inoperable cervical cancer should receive second-line chemotherapy outside of a clinical trial. Of course, the goal of clinical trial design and accrual is to discover safer and more effective treatments; however, the search for effective therapies must always be weighed against the impact on patient QOL. If physicians are honest with themselves (at this point in medical progress), the only good reason for considering a well-chosen treatment or a clinical trial for a patient with platinum-resistant disease is to reduce symptoms.

Decreasing symptoms is essential not only for improving QOL but also conceivably for prolonging survival. Chase et al[13] showed that the high Physical Well-Being domain of the FACTCX QOL survey was the only predictor of improved overall survival (OS) ($P<.001$) in clinical trials for recurrent, unresectable cervical cancer. Retrospectively noted, worsening physical symptoms and low physical functioning scores correlated with decreased survival.[13,14] Whether improvements in QOL while on cytotoxic or targeted therapy are from therapy or supportive care alone is unclear. As noted by Temel et al,[15] access to palliative (supportive) care in patients with incurable metastatic non–small cell lung cancer led to improvements in QOL, mood, and survival (11.6 vs. 8.9 months). In other studies, enrollment in hospice itself was associated with prolonged survival.[15,16]

Symptom Control in Patients With Incurable Cancer

The most important questions in caring for a woman with recurrent cervical cancer are, "Are her symptoms controlled?" and "Is her quality of life as good as it could be?" ASCO has recommended that palliative care be considered early in the course of care for patients with (all) metastatic cancers and for those with a high burden of cancer-related symptoms.[17] Therefore, regardless of decisions to administer second- or third-line treatments, palliative/supportive care should be actively requested by the oncologist and then initiated by a physician-led palliative care service that specializes in addressing distressing symptoms. After maximum QOL is achieved, treatment options can be considered. The question remains whether cytotoxic/targeted therapy should be offered at all at this point if no significant opportunity exists for symptom improvement.

Maximizing QOL, performance status, and symptom control is of primary concern regardless of plans to initiate additional therapy. The benefit and risk of any treatment is affected by a great number of variables, including age, socioeconomic factors, tobacco use, and psychosocial factors. Discussions relating to cytotoxic treatment for unresectable, unradiable cervical cancers should also address these issues, along with pain, lymphedema, tumor odor, and the benefits and disadvantages of a permanent PCN. Psychological and, more recently noted, financial distress should be addressed by simple surveys; the most easy to use is the Distress Thermometer, and patients should be triaged accordingly.[18] A simple question from a care team member, "How are you coping?," may identify additional areas of psychological and spiritual distress.

A comprehensive review of the management of symptoms is beyond the scope of this article. Many good palliative care references are available, but few

are specific to gynecologic cancer.[19] Common symptoms include:

- Lower extremity edema[20]
- Fistulas[21–23]
- Odors[24]
- Fatigue[25,26]
- Pain[27,28]
- Constipation[27]

Unfortunately, patients with cervical cancer, because of its association with low socioeconomic status, are often without the extensive social and clinical supportive services that are available to women with other cancers. Supportive treatment options for these women might be restricted because of limited "charity" resources and social isolation. Importantly, these women, often of minority status, need culturally appropriate discussions designed to build a foundation of trust in the patient-caregiver relationship, foster effective communication, and obtain informed consent. These patients need a health care team that includes a social worker, a translator, a case manager, and possibly a member of the clergy and/or a therapist; in other words, a palliative care team. This multifaceted approach is essential in treating cervical cancer, possibly more so than in any other cancer.

Quantifying Benefits of Treatment

Although few can argue that chemotherapy is beneficial when used to sensitize cervical cancers to radiation, the efficacy of chemotherapy in recurrent unresectable cervical cancer is limited. Despite some improvements in RR and duration of progression-free survival (PFS), only the combination of cisplatinum and topotecan has been associated with prolongation of OS (a minimal increase of 3 months).[29] A separate comparison of effectiveness of chemotherapy doublets in the first-line setting showed RRs ranging from 23% to 29% and a median OS ranging from 7.62 to 12.25 months.[1] No patients experienced cure. Although QOL was unaffected by the doublet used, no directed effort emerged that specifically addressed physical, psychological, social, and spiritual components of QOL.[30] Importantly, no randomized study in women with cervical cancer to date has included a best supportive care intervention, such as those performed in patients with non–small cell lung cancer.[31]

The use of second- and third-line therapy in women with recurrent cervical cancer, in the absence of real potential for symptom control, invokes the concept of futility and the Hippocratic mandate to "do no harm." Although QOL was not significantly affected in the GOG 204 trial, effects of treatment on QOL have been much more serious in other studies.[32,33] In these settings, defining futility is difficult and requires analysis of physiologic (RR), qualitative (QOL/symptoms), and quantitative (time) ineffectiveness, and surely financial consequences (to the patient, her family, and the health care system).[34] Some antiangiogenic targeted therapies have shown clinical RRs (10%–34%) in heavily pretreated patients with cervical cancer.[35–37] Unfortunately, most tested targeted agents have shown little to no significant response, and in some cases were associated with significant side effects.[32,37–41]

Determination of any particular treatment's ability to be marginally meaningfully effective is influenced by and reflected in the hopes, goals, symptoms, comfort, communication skill, and knowledge of the physician and patient (and her family). Conflict of interest and coercion of emotions between physician and patient, and patient and family, are important influences to identify, expose, and discuss, as are those related to financial factors (eg, price of treatment, out-of-pocket expense, and loss of work cost).

Decision Aids in Treatment Planning

Sentinel events have been described in women with ovarian cancer and assist with survival prediction, but similar events have not been defined in women with cervical cancer.[34] Gynecologic oncologists have seen some patients with immeasurable but extensive disease survive much longer than expected. What oncologists and patients and their families need are specific and objective clinical decision aids that put some order to a highly complex emotional decision. Decision aids have shown that concrete descriptions of clinical scenarios help patients understand the relative benefits and risks, resulting in lower percentages of patients choosing adjuvant chemotherapy (decreasing from 87% to 58%) and believing that they could be cured (decreasing from 52% to 31%).[42] Importantly, providing this information did not increase distress or decrease hope.[43] The gynecologic oncology community should focus on improving identification of wom-

en whose cervical cancer is most likely to respond to therapy and then incorporating the identified factors into cervical cancer treatment decision aids to guide decisions through this difficult time.

So what is currently known? It is known that, in terms of cure, the only group of previously irradiated women with recurrent cervical cancer that seems to benefit significantly from chemotherapy or surgery are those with isolated lung metastasis or solitary tumors recurring outside the irradiated field.[44] Moore et al[45] showed retrospectively that African American race, performance status greater than 0, pelvic disease, prior treatment with a radiosensitizer, and interval from diagnosis to first recurrence of less than 1 year are all independently predictive of poor response to first-line cytotoxic therapy. Patients with 4 to 5 risk factors had an RR of only 14% and median PFS and OS of 2.8 and 5.5 months, respectively, in trials using platinum-based therapy. It should be noted that the African American race was not supported as a prognostic factor in a multivariate analysis. Moore et al[45] recommended that these high-risk women should be given primary consideration for nonplatinum chemotherapy or targeted treatment trials. The authors also noted that "event limited toxicity, in the face of non-response to treatment or disease progression, is unacceptable…it is a clinical and ethical imperative to avoid adverse effects."[45] Gynecologic oncologists' efforts, as a community, should include studying these and other high-risk factors, and molecular predictors, at second and third recurrences to assist with the development of response predictions.

Doctor-Patient Candor

A tool designed to support treatment decisions for patients with cervical cancer should be a modification of the ASCO decision aids.[46] Decision aids can help remove some degree of conversation framing and discomfort, and objectively show the patient the potential risks and benefits of choices. Putting known response predictors and RRs in writing may help reduce the belief that cure is possible, a belief held by 69% to 81% of patients with incurable cancer.[47] The tool may also help guide the patient to "get her affairs in order" and determine how to best spend the precious time remaining.[43] After an honest discussion, assisted by a decision aid, the patient and physician can focus on the immediate problems detracting from QOL, including complications such as deep vein thrombosis, lymphedema, malodorous discharge, and pain, and psychosocial issues such as emotional and family distress. In this era of informed consent, it would be difficult and unethical to proceed with relatively ineffective treatment without informing the patient of risks and prognosis; this includes honestly reporting potential (or lack of) RR. A patient's wish to not know her prognosis can be approached by gently discussing probable outcomes and average duration of response.[48] The ASCO decision aid begins with the question, "Are you willing to view numbers or statistics which may predict the course of advanced cancer?" The question is followed by, "If you check no, it is recommended that you not use this decision aid."[46]

It is important for the woman to know that only a small portion of participants will gain any clinical benefit from participating in a clinical trial and that she most will likely experience progressive, or at best stable, disease. She should know that she may be spending precious time on the proposed trial without significant benefit to her. She should understand that the "science" will benefit more than she will from her participation. The honest, high-quality, conflict-free relationship implied by this sharing of information is integral to providing good and ethical care to patients with cancer in a setting of incurable disease. Admittedly, this information is very difficult to share.

Integrating Psychosocial Factors

Because of the low income and low educational attainment of many women with advanced cervical cancer, factors that may contribute to psychosocial distress include poor coping skills, depression, anxiety, lack of social support, drug use, chronic illnesses, and worry about young children. Although this has not yet been fully explored in the cancer population, studies of women with cervical dysplasia suggest that guilt, self-neglect, and fear may contribute to overall psychosocial distress.[49,50]

These issues are extremely relevant, because clinical and epidemiologic studies have recognized that behavioral factors such as stress, chronic depression, and lack of social support are risk factors for the development and progression of cancer.[51] Researchers are just beginning to characterize the molecular mechanisms through which behavior impacts tumor growth.[52,53] Imposed behavioral stress can result in increased levels of tissue catecholamines, increased

tumor burden, and increasingly invasive patterns of ovarian, lung, and colon cancer growth in orthotopic mouse models.[54–56] These effects are mediated primarily by elevation of noradrenalin, adrenalin, cortisol, and vascular endothelial growth factor (VEGF) via β-adrenergic receptor activation. The impact of the stress response may be particularly relevant in patients with cervical cancer because they often present with greater disruptions of QOL than patients with other types of cancer.[57–60] In fact, stress may play a strong role in the development of cervical dysplasia.[48,49,61] This is extremely important to consider in the care of women with cervical cancer as further progress is made in understanding the relationships among psychological distress, QOL, immune function, and OS.[62–64]

Targeting Stress and VEGF Pathways to Cancer

Recently, interest in the role of adrenergic blockade in the treatment of cancer has gained momentum. This attention originates from 1) studies showing that chronic stress results in physiologic alterations[51–53]; 2) retrospective studies indicating that use of β-blocking antihypertensive agents are associated with improved survival and that the presence of β-adrenergic receptor (ADRB) correlates with prognostic indicators in certain cancers[65–67]; and 3) in vitro and animal studies describing anticancer signaling activity, including reduction of serum and tumor VEGF levels, with the use of β-blocking agents.[54–56,68–73] In some cells, the effects of stress-induced expression of angiogenic factors can be abrogated by β-blockers. Based on this support, studies incorporating β-blockers in the treatment of cancer in humans are underway (www.clinicaltrials.gov). Ramondetta et al[74] found that 85% of cervical cancer samples tested had increased ADRB1 expression and 61% had increased ADRB2 expression.

Adrenergic blockade may affect survival in several ways, such as through

- Decreasing angiogenesis via VEGF and matrix metalloproteinase[54]
- Decreasing prometastatic immune response (eg, interleukin-8)[75]
- Decreasing adrenergic stress[76,77]
- Decreasing symptoms such as cachexia[78]

Conclusions

Ideally, treatment for incurable recurrent cervical cancer should focus primarily on decreasing symptom burden and improving QOL. All treatments for unresectable recurrence are palliative, although a short-lasting response may be expected in some patients. In these cases, cytotoxic treatment may be reasonable and should be considered. Although prolonging survival is the goal, promising therapeutic developments are limited, and thus efforts to improve QOL using supportive care strategies to relieve symptoms and distress should be the most important therapeutic goal for women with incurable cervical cancer. Decisions to proceed with palliative chemotherapy should be based on medical knowledge of predictors of response and honest disclosure to patients of RR and survival estimates. Discussions with patients should include detailed information regarding side effects of chemotherapy and should in most cases include a recommendation to forgo second- or third-line chemotherapy unless in the setting of a clinical trial. All women with recurrent cervical cancer should be referred to supportive care providers. Goals of trial design should include not only molecular targeting but also supportive care objectives, such as reducing pain, anxiety, depression, cachexia, and fatigue. A β-blocker could potentially be part of these intervention trials. The question of whether to administer second- and third-line chemotherapy should focus first on the concept "primum non nocere."

The question remains whether 9 months of palliative chemotherapy helped this patient. This may never be known for certain without a treatment trial for recurrent cervical cancer that includes a "no treatment"/best supportive care arm. Identification of response prognosticators and development of a decision aid for patients considering second- and third-line therapies should be a priority. With this type of evidence, women desiring treatment could then be given more accurate information regarding clinical trial benefits, and perhaps gynecologic oncologists could also be more honest with themselves.

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