Effect of a Beta Adrenergic Blockade combined with Relaxation/Guided Imagery Audio Intervention on symptom distress in Women with Advanced, Recurrent Incurable Cervical Cancer-Feasibility study

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SCHEMA

Blood drawn prior to administration of Propranolol after consented for study
Fill out questionnaires
Instruct on use of R/GI MP3 use and diary

Propranolol 20mg po bid initiated
Patient instructed to listen to MP3 2x a week and record in diary

Increase propranolol to 40 mg po bid if the patient is tolerating at one month time point.
Continue oral Propranolol until removal from study

Blood drawn and completion of questionnaires after the completion of every two cycles (2 mos and 4 mos)

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1.0 OBJECTIVES

1.1 Primary Objectives:

1.1.1 To determine the proportion of patients completing symptom inventory, anxiety and depression survey, pain inventory, and quality of life surveys (MDASI, HADS, BPI, FACT-Cx).

1.1.2 To determine the proportion of patients completing combined intervention of twice daily beta blocker use and twice weekly relaxation and guided imagery (R/GI) at two time points (2 mos and 4 mos).

1.2 Secondary Objectives:

1.2.1 To index cervix cancer specific symptomatology in this population and the serial change over intervention.

1.2.2 To determine the impact of beta blocker and R/GI on symptoms, anxiety and depression, pain, and quality of life (MDASI, HADS, BPI, FACT-Cx)

1.3 Exploratory objectives

1.3.1 To measure changes in serum levels of IL-6, IL-8, IL-10 and VEGF, CRP during treatment with propranolol in addition to receiving PMR intervention

1.3.2 To measure changes in resting energy use during treatment with propranolol in addition to receiving PMR intervention

1.3.3 To measure HPV components (e.g.E6 or E7 are reduced following treatment with beta blocker) in circulating cell-free DNA during intervention as a quantative assessment using qRT-PCR.

2.0 BACKGROUND AND RATIONALE

2.1 **Women should not die of cervical cancer…but they do.** Most cases of the disease are preventable, and it is highly curable if caught early. The primary cause of cervical cancer is HPV[2]. Furthermore, worldwide, cervical cancer is the second most common cause of cancer deaths in women [1]. In 2007, 12,280 women in the United States were diagnosed with cervical cancer, and more than 4000 died of it [1]. Furthermore, an estimated 530,000 cases of cervical cancer were diagnosed and 275,000 patients died of the disease in 2008, underscoring the tremendous loss of life attributable to cervical cancer [2]. Most importantly, chronic multidimensional pain is a prominent aspect of survival in cervical cancer patients [3-5]. The pain is often a combination of symptoms from direct pressure

from a mass, pain from nerve involvement of tumor or residual platinum induced neuropathy, pain from lymphedema and possibly from percutaneous nephropathy tubes.

Very few, if any, reports in the literature suggest that long-term complete clinical remission is possible in patients with advanced, recurrent, or metastatic cervical cancer [6-8]. Moreover, in all of the patients in these studies, if a complete response occurred, it did so during the first use of chemotherapy for recurrence. The use of second- and third-line therapy in such patients invokes the concept of "do no harm." In other words, if use of these therapies has no chance of improving survival and possibly no chance of even increasing overall QOL, then why continue to administer them? Possible explanations are that writing a prescription may be easier than facing the realities of this tragic situation and some physicians may themselves have a false hope of prolonging life. More likely, this treatment originates from a deep desire to help but with a dearth of effective tools to do so.

Although few can argue that chemotherapy is beneficial when used to sensitize cervical cancers to irradiation, chemotherapy for cervical cancer outside of this use is controversial. Despite some improvements in response rates and duration of progression-free survival, only the combination of cisplatin and topotecan has been associated with prolongation of OS; specifically, use of this combination resulted in a median OS duration of 9.4 months compared with 6.5 months in patients who received cisplatin only ($p = .017$)[9, 10]. Unfortunately, with increased use of cisplatin for radiation sensitization, more recurrent cervical cancers seem to be resistant to cisplatin [10, 11]. For example, the overall response rate in patients in GOG 179 who previously received cisplatin for irradiation sensitization was 13% compared with 27% who had not [9, 11].

The Gynecologic Oncology Group (GOG)-204 protocol compared the four most effective chemotherapy doublets in treatment of recurrent cervical cancer in patients with no prior treatment of recurrences. The response rates ranged from 23% to 29% [10]. No patients in the GOG-179 or -204 study experienced cures despite having slight increases in their PFS. In these studies, although QOL was unaffected by the doublet used, no detailed assessment was done that addressed any of the components of QOL, including physical, psychological, social, and spiritual QOL. Furthermore, there has yet to be a trial for women with recurrent cervical cancer involving a "no chemotherapy/best supportive care" arm.

Some anti-angiogenic targeted therapies for cervical cancer have demonstrated clinical response rates in heavily pretreated cervical cancer patients (10-34%) [12, 13]. Unfortunately, the majority of tested targeted agents, including cetuximab and single agent premetrexed (alimta) (13.9% RR and SD stable disease 53%), and erlotinib had little to no significant response and in some cases were associated with significant side effects. For expensive agents such as

bevacizumab, until significant improvement in PFS and OS is demonstrated, their use will most likely be restricted to clinical trials.

We know now that more than 70% of incurable cancer patients believe their cancer is curable when receiving chemotherapy and that these beliefs prevent patients from entering into hospice/palliative care [14]. This is unfortunate, as we have since learned from Temel and colleagues, who explored the benefits of early palliative (supportive) care in patients with incurable metastatic non-small cell lung cancer, that early palliative care not only leads to improvements in QOL and mood but also improves survival. In their study, the median survival duration was 11.6 months versus 8.9 months in those who received earlier palliative care interventions [15]. The reason for the survival improvements gained from early palliative care include the improvement of medical comorbidities, facilitation of the receipt of effective chemotherapy as well as avoidance of detrimental cancer treatments. Although little is known about women with cervical cancer, depressed cancer patients have been shown to have worse survival and that improvement in these symptoms, not specific to any treatment, has been associated with increased survival [16, 17]. Although early palliative care has also been associated with less depression but at this point, lessened depression does not appear to mediate the survival benefit gained [15, 18].

The goal of future therapeutic trial design is to develop and evaluate a less expensive and safer method of inhibiting angiogenesis in recurrent cervical tumors. During this search, we must balance the search for effective therapies with the potential for side effects that can negatively impact QOL. In fact, members of the GOG have suggested that new targeted agents perhaps should not even be evaluated in women unfortunate enough to have recurrent cervical cancer owing to its predicted dismal response rate, worsening of QOL in patients who have it, and the possibility that a promising therapeutic targeted agent may be dismissed as ineffective because of lack of effect response rate (personal communication). Although improved survival duration is the goal, supportive care and efforts to improve QOL with early triaging and relief of symptoms and psychosocial difficulties is now recognized as the most important goal for patients with incurable advanced cervical cancer [19].

2.2 Neuroendocrine Stress Response

Stress is a complex process consisting of environmental and psychosocial factors that initiate a cascade of information-processing pathways in both the peripheral and central nervous system [20, 21]. These stress pathways elicit the “fight-or-flight” stress responses in the autonomic nervous system or “defeat/withdrawal” responses produced by the hypothalamic-pituitary-adrenal axis. Activation of these pathways prepares a person to endure a threat. However, under chronic stress, most organs are negatively affected by prolonged exposure to glucocorticoids and catecholamines resulting from the stress. Until recently, stress was known to increase the risk of cardiac disease and infection [22]. Now, an

increasingly clear finding is that chronic changes in neuroendocrine dynamics can alter various physiological processes, such as adhesion of tumor cells to the extracellular matrix, cancer cell migration and invasion, angiogenesis, and cell survival, all of which are critical to tumor biology and pathogenesis [23]. Although most of the data collection regarding the immunohistochemical expression stress receptors has been performed in breast and ovarian cancer tissue, supportive data suggest that the neuroendocrine stress response is important to other cancers, as well.

2.3 Psychosocial Factors and Cancer

Researchers have long suspected that psychosocial factors play significant roles in malignant progression [21]. Clinical and epidemiological studies have recognized that behavioral risk factors such as stress, chronic depression, and lack of social support are risk factors for the development and progression of cancer. Also, increasing evidence indicates that psychosocial interventions improve the QOL of cancer patients although the effects of these interventions remain controversial [24, 25]. Studies have inconsistently demonstrated a relationship between behavioral risk factors and cancer initiation. However, researchers are just beginning to characterize the molecular mechanisms by which behavior impacts tumor growth [20]. Recent laboratory work demonstrated that imposed behavioral stress results in increased levels of tissue catecholamines, an increased tumor burden, and an increasingly invasive pattern of ovarian, pancreatic, and colon cancer growth in orthotopic mouse models of these cancers [23, 26-28]. These effects are mediated primarily by elevation of noradrenalin, adrenalin, cortisol, and vascular endothelial growth factor (VEGF) levels via β_2-adrenergic receptor activation of the tumor cell cyclic AMP-protein kinase A signaling pathway [23, 26]. Supporting this finding, Lutgendorf and colleagues analyzed 10 ovarian carcinomas in patients with high depressive symptoms and low social support compared with patients at low levels of depressive symptoms and found increased activity of several β-adrenergically linked transcription control pathways, including the cyclic-AMP response element-binding protein/activating transcription factor and proinflammatory signal transducer and activator of transcription family of transcription factors [29], thereby confirming the importance of direct neuroendocrine regulation of tumor cell biology established in the *in vivo* orthotopic model [23]. Lutgendorf's group also suggested that immune function can be preserved using integrative medicine/healing touch intervention with resultant preservation of natural killer (NK)-cell cytotoxicity [30]. Tumor response to treatment may also be affected by physiological stress, as stress hormones can interfere with chemotherapeutic efficacy and contribute to drug resistance [31] and may even be blocked by β_2-adrenoceptor blockers [32].

2.4 Targeting stress and VEGF pathways to cancer?

Recently, interest in the role of adrenergic blockade in treatment of cancer has gained momentum. This attention originates from 1) studies demonstrating that

chronic stress results in physiological [21, 23, 33]; 2) retrospective studies indicating that use of beta-blocking anti-hypertensives is associated with improved survival and that the presence of adrenergic receptor beta (ADRB) correlates with prognostic indicators in certain cancer subtypes; and 3) *in vitro* and animal studies describing anticancer signaling activity, including reduction of serum and tumor VEGF levels with the use of beta adrenergic blocking agents [34-38]. In some cells, the effects of stress induced expression of angiogenic factors can be abrogated by beta-blockers.

Retrospective data on cohorts of ovarian as well as breast cancer patients has suggested that the use of beta-blockers significantly reduces the risk of death. Others have shown improved relapse-free survival intervals in patients with triple-negative breast cancers and in patients with melanoma using beta-blockers Researchers have identified ADRB in breast, pancreatic, ovarian, lung, head and neck, prostate, and colon cancer cases

Adrenergic blockade may affect survival in a number of ways

- Decreasing angiogenesis via VEGF, MMMP (33)
- Decreasing a prometastatic immune response (Il8)
- Decreasing adrenergic response [39, 40]
- Decreasing symptoms such as cachexia [41]

To date, four studies of the use of beta-blockers for treatment of cancer in humans are under way. [http://www.clinicaltrials.gov].

2.5 Physiological and Psychological Stress and Cervical Cancer

Due to the association of low income and low levels of education, potential factors that may contribute to psychosocial distress in women with cervical cancer include poor coping tools, depression, anxiety, lack of social support, drug use, comorbidities besides cancer (other chronic illnesses besides cancer), as well as having young children. Furthermore, but not yet fully explored in the cancer population, clinical trials of women diagnosed with cervical dysplasia suggest that guilt, self-neglect, and fear may contribute to overall psychosocial distress. These issues are extremely relevant as clinical and epidemiological studies have now recognized that behavioral risk factors such as stress, chronic depression, and lack of social support are risk factors for the development and progression of cancer [21]. The impact of the stress response may be particularly relevant in cervical cancer patients because they may often present with greater disruptions of QOL than patients with other types of cancer[23, 33]. In fact, stress may play a strong role in the development of cervical dysplasia. This is extremely important to consider in the supportive care of women with cervical cancer as we begin to make further progress in our understanding of the relationships between psychological distress, QOL, immune function and overall survival.

For example, Pereira showed that in human immunodeficiency virus-positive women, increased life stress correlated with progression and persistence of cervical neoplasia [46]. In a small study of patients with cervical dysplasia, patients with dysplasia and healthy controls had significant differences in cortisol levels [47]. Pereira et al. suggested that psychoneuroimmunological mechanisms play a role in human papillomavirus (HPV)-mediated cervical neoplasia, the initiation point for development of invasive cancer [46]. Psychoneuroimmunological changes in patients with early cervical cell transformation emphases effect on the regression and disappearance of HPV via a cell-mediated immune response involving T helper type 1 (TH1) cells, NK cells, and interleukin (IL)-10 [48, 49]. With inadequate immunity, HPV infection may become persistent. In addition, cigarette smoking may contribute to HPV infection via correlation of progression with increased serum cotinine concentrations [49].

2.6 Symptom distress assessment and interventions in cancer patients

Supportive care and symptom control are important aspects in the care of a woman with incurable cervical cancer. All too often, care is focused on treatment interventions to potentially lengthen life without equivalent intense focus on improving symptom control.

One of the few stress interventions reported in a population of cervical cancer patients was in a randomized trial in cervical cancer survivors [50]. The survivors underwent psychosocial counseling sessions over the telephone, whereas the controls underwent “usual care.” The patients completed six counseling sessions of about 45-50 minutes in length in their preferred languages. The sessions consisted of five consecutive weekly sessions and a booster session delivered by a psychologist. QOL data and biological specimens were collected at baseline and 4 months after enrollment. Significant improvements in QOL were noted in the intervention arm and these improvements were associated with significant immune system changes, most notably an increase in the TH1:TH2 cell ratio. The authors concluded that “the integration…interventions leading to enhanced QOL could result in improved clinical outcome including survival” [50]. Similar studies of other cancer types suggested that relaxation interventions can improve overall survival in patients with other types of cancers [51]. Importantly, Lutgendorf’s group showed that immune function can be preserved in cancer patients with integrative medicine/healing touch (stress reduction) intervention and resultant preservation of NK-cell cytotoxicity [30].

Few non pharmacologic QOL interventions have been performed in advanced cancer patients. Psychological interventions may help cancer patients in a variety of ways, including reducing the severity of side effects of cancer and its treatment, anxiety, and distress, and more recently, these interventions have been linked with improved immune function which may result in “improved OS durations” [30, 50, 51]. Interventions have included a variety of methods including telephone support and psychological counseling [52, 53]. Many of these

approaches are time consuming and not practical for patients nearing the end of life.

Most studies evaluating the effectiveness of psychological/behavioral interventions are limited by poor methodology. A recent systematic review assessing randomized controlled trial designs using evaluated internal validity indicators suggested that the quality of such studies is suboptimal [54] That said, authors have reported psychoneuroimmunological effects of relaxation/guided imagery interventions such as improved behavioral/coping metrics, including improved mood and decreased anxiety, nausea, vomiting, and anger but also decreased levels of cortisol, IL-6, IL-10, and IL-12 and activity of NK cells and other immune modulators. Relaxation and guided imagery (R/GI) is a form of relaxing meditation in which involves systemic tensing and relaxing of various parts of the body progressing from feet to head. Through guided imagery, patients listen to recorded and/or spoken speech of specific positive thoughts associated with calmness, control and reduction of distress.

Relaxation and Guided Imagery (R/GI) for reduction of distressing symptoms in cancer populations has been seen in multiple studies [55] [56, 57]. However, some have reported mixed results for the relief of anxiety and depression in people with cancer [58-60]. Importantly, impressive results have been reported in a group learning relaxation and imagery techniques for management of anxiety and discomfort during brachytherapy [61]. The patients received training and relaxation and guided imagery for 10 min and were given a cassette to use at home and in hospital. In lung cancer patients undergoing radiation distressing symptom clusters include breathlessness, and anxiety and fatigue, thought to originate from a “stress” trigger [62]. During the 12 week study, the intervention involved a 40 min educational package plus coaching. An audiotape was also provided to patients and they were asked to listen daily. Significant effects on breathlessness, fatigue, anxiety and functional ability were found [57]. In a feasibility study of 86 patients, sessions lasted 90 minutes and held weekly for 6 weeks [55]. An improvement was seen in both impact of events scale and brief symptom inventory [55].

R/GI has also been used to address pain in cancer patients. Kwekkeboom et al were able to show improvements in pain intensity, pain-related distress, and perceived control over pain using R/GI but little other data is available in this population [63]. Additional support for this method is detailed in Bonica's Management of Pain [64].

Immunomodulating effects as reported in the Nelson study [50] required extensive interventions such as time consuming phone call commitments and those described in Jon Cabot-Zinn’s mindfulness meditation curriculum, which includes an 8-week review of the benefits and techniques of mindful meditation as well as recommended daily homework [65, 66]. Nelson and colleagues conducted six counseling sessions 45-50 minutes in length (five consecutive weekly sessions and a booster session 1 month after completion of sessions. Most studies suggest that

active/experienced mind-body practice techniques (e.g., mindfulness meditation) can be more effective than less/novice practiced techniques [67, 68].

The literature contains insufficient data to support the exact "dose" in a relaxation stress-reduction intervention [65, 69, 70]. It does contain data supporting good results with experience and increased frequency and duration of practice, but the dose at which such results are obtained remains unknown. According to available data, results require practice most days of the week and sessions at least 20-30 minutes long [20, 67, 68, 71-73]. Most studies showing the effectiveness also demonstrate that reminder phone calls and instruction to practice these interventions daily at home are effective [50, 65, 72].

The present study is designed to evaluate the effect of β-adrenergic blockade and R/GI on advanced incurable cervical cancer. The reason for this Phase II feasibility study design is based on the following:

1. The best clinical practice in these patients is to offer a supportive care consultation if available for symptom control regardless of therapy offered

2. There is concern regarding the feasibility and acceptability for patients nearing the end of their life to accrue to a trial that doesn't use a new agent as its targeted intervention, this design will allow assessment of feasibility/acceptability.

3. Beta blockades have not been used in a clinical population nearing the end of life and with advanced cancer and tolerability will need to be assessed. This trial will allow for an upward titration of B blockade with close observation of BP and Pulse.

4. R/GI will allow for additional QOL benefits for these patients at this important time point and will allow the evaluation of the combination on translational end points and then allow us to proceed with planned randomized phase II to tease out the individual influences.

2.7 β-Adrenergic Receptors and Their Roles in Cancer Development

Four β-adrenergic receptors (bARs) exist, and they have been characterized according to their physiological functions. bARs are G protein-coupled receptors that are the targets of catecholamines such as norepinephrine and epinephrine and whose primary function is to transmit information from the extracellular environment to the interior of the cell, leading to activation of adenylyl cyclase and accumulation of the secondary messenger cAMP [20]. β_1-adrenergic receptors have chronotropic effects (affecting the heart rate and thereby increasing cardiac output), release renin, and increase lipolysis. β_2-adrenergic receptors cause dilation of blood vessels and bronchioles, stimulate insulin release, and increase lipolysis, glycogenolysis, and gluconeogenesis. β_3-adrenergic receptors

are involved in lipolysis and mediate vascular relaxation but are activated by higher concentrations of catecholamines. Researchers have identified bARs in breast, pancreatic, ovarian, lung, head and neck, prostate, and colon cancer cases [34-38, 74-76]. Palm and associates found that 70-90% of human tissue microarray specimens of breast, colon, and prostate tumors expressed β_2-adrenergic receptor and demonstrated using an *in vivo* model that the incidence of lymph node metastases increased with the administration of norepinephrine but decreased with the introduction of the β-blocker propranolol [37]. Until recently, whether the direct neuroendocrine regulation of tumor cell biology demonstrated convincingly in *in vitro* and *in vivo* ovarian cancer models is biologically relevant to primary human tumors as well as whether the regulation correlated with biobehavioral characteristics was unclear [34]. In 2009, Lutgendorf and colleagues explored this relationship by identifying human ovarian tumor specimens that had high (high depressive symptoms and low social support; n = 10) versus those with low (low depressive symptoms and high social support; n = 10) biobehavioral risk profiles [29]**.** They found that gene expression profiles in primary ovarian tumor specimens are systematically altered in association with the patient's biobehavioral risk factors, and promoter-based informatics analyses confirmed that β-adrenergic transcription control pathways are the key mediators of differences in gene expression profiles. Additionally, tissue levels of the sympathetic catecholamine norepinephrine were elevated in ovarian tumor specimens obtained from patients with high biobehavioral risk profiles [77].

Studies of other cancers support the importance of bARs in cancer progression. Importantly for our proposed study, oral squamous cell carcinoma (potentially HPV-related) cells highly express β_2-adrenergic receptor, and its expression is significantly correlated with lymph node metastasis and advanced tumor stages cancer patients [75]. Also, regarding the connection between smoking and cervical dysplasia, researchers have noted that nicotine promotes gastric, pancreatic, lung, esophageal, and colon tumor and melanoma growth and anti-angiogenesis via β-adrenergic activation (β_2-adrenoreceptors with subsequent stimulation of cyclooxygenase-2, prostaglandin E_2, and VEGF) [76, 78-83].

2.8 β-Blockers

Propranolol is a first-generation β-blocker that non-selectively blocks both β_1- and β_2-adrenergic receptors. We selected this β-blocker for our proposal, because it is still commonly used and researchers have used it with an orthotopic mouse model of ovarian cancer [23, 75, 76, 81, 84]. Thaker and colleagues demonstrated that chronic behavioral stress resulted in increased levels of tissue catecholamines, an increased tumor burden, and increasingly invasive growth of ovarian carcinoma in that model. These effects appeared to be mediated by activation of the tumor cell cyclic AMP-protein kinase A signaling pathway by β_2-adrenergic receptor. These stressed mouse tumors had higher expression of angiogenic factors, including VEGF, than did control mouse tumors [85]. The effects of chronic behavioral

stress on expression of angiogenic factors can be abrogated by β-blockers, thereby emphasizing the importance of that trial in demonstrating the feasibility of adding the use of β-blockers to standard palliative approaches to treatment in and care for cervical cancer patients.

Recently, Diaz et al. [86] presented retrospective data on a cohort of ovarian cancer patients in whom use of β-blockers reduced the risk of death by 56% below that in nonusers. The data regarding the effectiveness of β-blockers may be most compelling in breast cancer patients [87]. For example, Powe et al. recently retrospectively studied breast cancer patients and showed that β-blocker–based therapy reduced the number of distant metastases, the incidence of cancer recurrence, and mortality rates, and others have shown that inhibiting the β_2-adrenergic signaling pathway can reduce breast cancer progression and mortality [87, 88]. Also, showed improved relapse-free survival durations in patients with triple-negative breast cancers using beta-blockers [89]. Furthermore, use of β-blockade in melanoma patients has received much recognition. Specifically, researchers demonstrated that use of β-blockers was associated with a reduced risk of progression of thick malignant melanoma and that β-blocker intake was associated with increased survival durations in melanoma patients [90, 91]. Laboratory data suggests that the effects of β-blockers on cancer cells are accomplished via blockade of adrenergic stimulation of increased noradrenaline, adrenaline, cortisol, and VEGF levels via β_2-adrenergic receptor activation of the tumor cell cyclic AMP-protein kinase A signaling pathway [26, 85].

2.9 Angiogenesis, VEGF, and Cervical Cancer

In patients with cervical neoplasia, VEGF expression and microvessel density progressively increased during the transition of normal cervical epithelium to squamous cell carcinoma [92]. Furthermore, polymorphisms of VEGF genes may correlate with survival of early stage cervical cancer by modulating angiogenesis as measured according to microvessel density [93]. In the animal laboratory model, increased tumor vascularization and enhanced expression of VEGF and matrix metalloproteinase-2 and -9 in tumor cells in stressed animals could be abrogated by the use of a β-adrenergic antagonist such as propranolol [23]. Extrapolating from this data and recognizing that the HPV-18 E6 oncoprotein induces VEGF transcription in a p53-dependent manner, decreasing the expression of VEGF in tumor cells by reducing the stress response may be an interesting method of cervical cancer therapy [94]. This is substantiated by the fact that VEGF receptor 2 is more highly expressed in cervical cancer cells than in normal cervical tissue controls [92, 93, 95]. High vascularity as measured according to microvessel density is associated with a positive lymph node status [96], poor prognosis, and increased risk of recurrence [97]. Five-year survival rates for cervical tumors with high and low microvessel densities are 50% and

65%, respectively [98]. Finally, serum VEGF levels are significantly elevated in cervical cancer patients with large and/or high-grade tumors or who smoke [95].

2.10 Cervical Cancer Cell Lines, Cervical Cancer Tissue, and Adrenergic Receptors

In our lab we evaluated human cervical cancer samples obtained at the time of diagnosis from 168 women. ADRB1 and ADRB2 expression was examined using immunohistochemical peroxidase staining and semi-quantitative scores were related to patient outcome. In addition, we examined the effects of catecholamines on production of pro-angiogenic factors (VEGF, IL8) by cervical cancer cell lines (SiHa and Caski) using qRT-PCR.

The median age of patients was 45.3 (range 22 – 83). Among the 168 tumor samples evaluated, 85% had increased ADRB1 expression and 61% had increased ADRB2 expression. Tumor stage or grade were not related to ADRB expression. ADRB1 expression was not related to overall patient survival ($p = 0.86$); however, ADRB2 was significantly related (mean 146 months for those with increased expression vs. 206 months for those with low or absent expression; $p = 0.038$). Upon stimulation with norepinephrine or isoproterenol, the levels of VEGF did not change appreciably, but the levels of IL8 increased by 3.5 – 6-fold ($p<0.001$). These data support the hypothesis that ADRB2 might play a pivotal role in cervical cancer growth and progression and have potential clinical implications for new therapeutic strategies.

2.11 Summary

Women diagnosed with recurrent cervical cancer are faced with a dearth of effective chemotherapy or other therapies in a recurrent setting; thereby, using a low side effect drug such as propranolol beneficial in a population with such a short time of overall survival is appropriate. There are many other downstream effectors of the beta-adrenergic receptor which are equally important in carcinogenesis that will need to be explored in the future.

Because β-blocker use has been prevalent in patients with cardiovascular disease for years, they are known to be safe and offer the relatively inexpensive opportunity to test our hypothesis regarding the effects of neurobiological stressors on cervical cancer in our proposed study. Our hypothesis is that the intervention of a beta-adrenergic blockade in conjunction with “minimal dose” relaxation intervention in advanced cervical cancer patients will result in stable to improved quality of life and improved overall survival. This improved QOL and OS will correlate with decreases in serum levels of interleukin 6 and 8 and VEGF. Furthermore, attention to QOL at the end of life has become of the utmost importance in caring for patients with advanced cancer. ASCO recently supported the emphasis on best supportive care in stating that “substantial evidence demonstrates that palliative care—when combined with standard cancer care or as

the main focus of care—leads to better patient and caregiver outcomes." These include improvement in symptoms, QOL, and patient satisfaction, with reduced caregiver burden. Earlier involvement of palliative care also leads to more appropriate referral to and use of hospice, and reduced use of futile intensive care [19] The proposed study emphasizes avoidance of treatment of recurrent incurable cervical cancer with standard second line therapies, in which response durations have been dismal. Instead, this proposal integrates an R/GI therapy intervention and low-risk treatment with a β-blocker, which is supported by strong preclinical and retrospective data and expected to result in maintained OS decreased distress and improved quality of life.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion:

3.1.1 Proven recurrent cervical cancer of any histology not eligible for curative radiotherapy or surgery.

3.1.2 Failed chemotherapy for first recurrence (excluding chemotherapy with concurrent irradiation) or refractory to first line systemic therapy.

3.1.3 Measurable or non-measurable disease

3.1.4 Unlimited prior therapies

3.2 Exclusion:

3.2.1 Patients whose disease may be cured by surgery or radiotherapy.

3.2.2 Contraindication to use of a β-blocker.(uncontrolled DM, COPD-unstable, Bradycardia <50 BPM)

3.2.3 Already receiving a β-blocker.

3.2.4 Performance status > 3. Must have had treatment for first line recurrence

3.2.5 Prior radiation therapy for localized cancer of the breast, head and neck, or skin is permitted provided that it was completed more than 3 years prior to registration, and the patient remains free of recurrent or metastatic disease.

3.2.6 With the exception of non-melanoma skin cancer and other specific malignancies as noted above, patients with other invasive malignancies who had (or have) any evidence of the other cancer present within the last five years or whose previous cancer treatment contraindicates this protocol therapy are excluded.

3.2.7 Use of systemic glucocorticoids such as Prednisone or Decadron in the last month for greater than one week

3.2.8 Inability to accurately answer questions (e.g. dementia, brain metastases) or speak English or Spanish.

3.2.9 Cirrhosis of the liver

3.2.10 Patients under the age of 18

3.2.11 History of comorbid conditions: Addison's disease, autoimmune hepatitis, hepatitis B, hepatitis C, AIDS or HIV, lupus erythematosus, mixed connective tissue disease, rheumatoid arthritis.

3.2.12 Hypersensitivity to propranolol, or beta-blockers

3.2.13 Uncompensated congestive heart failure

3.2.14 Cardiogenic shock

3.2.15 Severe sinus bradycardia; heart block, second or third degree or sick sinus syndrome (if no artificial pacemaker present)

3.2.16 Severe hyperactive airway disease (chronic obstructive pulmonary disease, asthma)

3.2.17 Any patients on Avastin or any other anti-angiogenic drugs.

3.2.18 Patients with brittle diabetes mellitus (DM) Brittle diabetes mellitus is a type of diabetes when a person's blood glucose (sugar) level often swings quickly from high to low and from low to high. Also called "unstable diabetes" or "labile diabetes."

3.2.19 Patients participating in or who plan to participate in other trials during the course of this study.

3.2.20 Patients actively using cocaine.

3.2.21 Cannot be receiving any other active neoplastic treatment during 4 months of study.

4.0 STUDY MODALITIES

4.1 Propranolol (Inderal^{R})

4.1.1 Indication and Use:
Used for treatment of hypertension, cardio protection after a myocardial infarction, and management of cardiac arrhythmias such as atrial fibrillation. Also it can be used in the treatment of migraines or essential tremor.

4.1.2 Formulation:
Propranolol is supplied as tablets in the following strengths: 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg.

4.1.3 Storage:
Store tablets at room temperature between 20-25ºC (68-77ºF) and away from light and moisture

4.1.4 Administration:
A starting dose of propranolol 20 mg is taken by mouth twice a day (40 mg/day). If the patient tolerates the initial dose (no hypotension or bradycardia) the dose will be increased to 40 mg by mouth twice a day at the start of the second month of therapy. For patients >65 years old the dose will stay at 20 mg by mouth twice a day. Dose reductions to 10 mg administered by mouth twice a day will be allowed for titration for optimization of BP and pulse. All dose adjustments will be made in the clinic.

4.1.5 Onset and Duration of Action:
Propranolol is administered orally or intravenously. After oral administration of immediate-release propranolol, the dose is almost completely absorbed, and peak concentrations are achieved within 60-90 minutes. Co-administration with food appears to enhance bioavailability.

Despite complete absorption, propranolol has a variable bioavailability due to extensive first-pass metabolism. Hepatic impairment will therefore increase its bioavailability. The main metabolite 4-hydroxypropranolol, with a longer half-life (5.2-7.5 hours) than the parent compound (3-4 hours) is also pharmacologically active.

4.1.6 Metabolism and Excretion:
Propranolol is highly lipophilic and, as a result, is widely distributed throughout the body. It readily crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Propranolol is greater than 90% bound to plasma proteins, primarily alpha-acidic glycoprotein which is elevated in conditions of physiological stress such as inflammation or cancer.

Propranolol is extensively metabolized upon first pass through

the liver by CYP2D6 isoenzymes, with secondary pathways via CYP2C19 and CYP1A2. The drug also binds to and saturates non-specific hepatic binding sites before the drug reaches the systemic circulation. An equipotent, pharmacologically active metabolite, 4-hydroxy-propranolol, is produced with the initiation of oral therapy, but it is eliminated faster than the parent drug because with chronic or IV therapy, this metabolite is produced to a lesser degree.

Excretion of propranolol occurs renally, primarily as metabolites, with only 1-4% of a dose excreted fecally as unchanged drug. The elimination half-life of propranolol ranges from 2-6 hours, with protein binding and chronic administration yielding longer half-lives, possibly due to saturation of liver binding sites and/or systemic clearance. In patients with severe renal dysfunction, fecal elimination may increase to compensate for decreased renal excretory processes. Propranolol is not appreciably removed by hemodialysis. Caution is recommended administering propranolol in patients with altered renal or hepatic function as well as in elderly population because of altered pharmacokinetics, specifically extended half-life/decreased elimination.

4.1.7 Drug Interactions: (www.clinicalpharmacology-ip.com)

Adenosine
Anti-arrhythmic drugs (flecainide, propafenone, moricizine, encainide)
Amiodarone
Bretyllium
Calcium-blocking blood pressure drugs such as diltiazem, nifedipine, and verapamil
Certain high blood pressure medications such as reserpine
Cardiac glycosides
Epinephrine
Insulin
Levodopa
Lidocaine
Monoamine oxidase inhibitors
Oral diabetes drugs such as glyburide
Prazosin
Quinidine
Rifampin
Theophylline

4.1.8 Contraindications and Side Effects:

The adverse effects of propranolol are generally mild and temporary. These side effects usually occur at the onset of therapy and diminish over time. Propranolol is contraindicated in patients with sinus bradycardia, cardiogenic

shock, bronchial asthma, or allergic to propranolol. Use with care in patients with congestive heart failure.

Side Effects: Sinus bradycardia, hypotension, AV block, congestive heart failure in patients with preexisting left ventricular dysfunction, depression, confusion, hallucinations; or Mask signs of hypoglycemia, Agranulocytosis, decreased sex drive, impotence, or difficulty having an orgasm; nausea, vomiting, diarrhea, constipation, stomach cramps; sleep problems (insomnia); or tired feeling.

Please refer to Appendix O & P - Common Side Effects of Beta Blockers.

4.1.9 Supplier:
Propranolol will be provided free of charge to the patients and distributed by the Mays Clinic Pharmacy, MD Anderson Cancer Center, and the LBJ Pharmacy. Patients will receive monthly supplies.

4.1.10 Pill Calendar Diary (Appendix M, N):
A pill calendar diary will be submitted at each visit along with the pill bottle for verification. Calendars, empty bottles and any unused medication will be collected at each appointment before the next refill is given to the patient.

4.1.11 Relaxation Practice Log (Appendix Q, R)
The relaxation practice log is to help keep track of relaxation practice. A relaxation practice log will be submitted at each clinic visit.

5.0 PROPOSED TREATMENT/STUDY PLAN

5.1 Dosing of Propranolol

A pill diary will be provided that is a monthly calendar on which patients will record the study medication they take each day. Every dose will be documented and if doses are missed, the patient will be asked to note why they missed a dose. Calendars, empty bottles and any unused medication will be collected at each appointment before the next refill is given to the patient.

Propranolol will be provided to the participant free of charge.

A starting dose of propranolol 20 mg is taken by mouth twice a day (40 mg/day). If the patient tolerates the initial dose (no hypotension or bradycardia) the dose will be increased to 40 mg by mouth twice a day at the start of the second month of therapy. This will ideally be titrated up to 40 mg twice a day in order to maintain a heart rate between 50 to 80 bpm without symptoms or hypotension (systolic BP <110 or diastolic BP <50). For patients > 65 years old the dose will stay at 20 mg by mouth twice a day. Dose reduction to 10 mg administered by

mouth twice a day will be allowed for titration for optimization of BP and pulse. All dose adjustments will be made in the clinic.

To insure compliance, patients will fill out pill calendar diaries that will be collected on a monthly basis.

If removed from study, all patients will be weaned off the medication over the following 2 weeks. The dose will be reduced by 50% for 7 days then will be reduced to 25% of the dose for 7 days then discontinue completely. For patients that experience adverse effects during weaning the period of time can be increased as deemed appropriate.

5.2 Relaxation Intervention

Three 20-minute audio relaxation/guided imagery (R/GI) exercises (MP3) will be provided to each patient (in English or Spanish). Patients will be instructed to listen to the MP3 two times a week and make recordings in a standard diary regarding whether they were able to complete the session and whether they had any difficulties in doing so (difficulties recorded in the diary should include lack of time, unexpected interruption, noise, the presence of children, and other distractions) [99]. To ensure compliance, patients will complete relaxation exercise activity logs as well as pill calendar diaries. These will be collected monthly. (Pill diary)

5.3 Methodology

After a patient is deemed eligible for the study, she will be asked to provide consent to participate. If consent is given, at this time the patient will be given a demographic questionnaire (age, race, marital status, and smoking history) and the Functional Assessment of Chronic Illness Therapy-Cervix (FACT-Cx), Brief Pain Inventory (BPI), MD Anderson Symptom Inventory (MDASI) and Hospital Anxiety and Depression Scale (HADS). Additionally, blood will be drawn from the patient in the clinic prior to the start of the intervention for measurement of baseline IL-6, IL-8, IL-10, circulating HPV DNA, and VEGF levels.

Upon enrollment, all patients will be instructed to listen to MP3-relaxation/guided imagery audio intervention. Patients on protocol will be referred for supportive/palliative care consultation at MDACC or LBJ. At the end of four months, patients will have the option of continuing treatment until intolerability of the treatment, disease progression or death. *Propranolol will be provided to the participants free of charge. Propranolol will be administered at 20 mg twice a day (40 mg/day). This dose will ideally be titrated up to 40 mg twice a day to maintain a heart rate of 50-80 beats per minute without causing hypotension (systolic blood pressure [BP] < 110 mmHg or diastolic BP < 50 mmHg). For patients more than 65 years old, the starting dose will be 20 mg given by mouth twice a day. Dose reduction to 10 mg administered by mouth twice a day will be allowed for titration for optimization of BP and pulse*. All dose adjustments will

be made in the clinic. Blood draws and completed surveys of biobehavioral measures (FACT-Cx, MDASI, HADS, BPI and smoking history) will be collected at baseline and again after the completion of every two cycles (1 month = one cycle) until the 4-month time point. The HADS will be scored and evaluated within 24 hours of completion. The Hospital Anxiety and Depression Scale (HADS) is a 14 item self-administered scale to detect states of depression and anxiety. Respondents answer questions using a scale of 0 (not at all) to 3 (very often). A HADS score of 15 or higher defines clinical depression or anxiety, and those patients will be assessed by their physician, and, if appropriate, referred to psychiatry. Scoring will be done by the research personnel.

Feasibility is determined by completion of three time points (TP0, 2, 4 mos). Patients who wish to continue on the regimen may do so until voluntary discontinuation, intolerability, disease progression, or death. The patient will be followed until death with assessment of medical notes in clinic station. Reason for study termination will be recorded.

CT of chest, abdomen, and pelvis will be obtained at baseline within 6 weeks prior to starting treatment and then per MD discretion or worsening of symptoms.

5.4 Quality of Life Analysis

5.4.1 Functional Assessment of Chronic Illness Therapy-Cervix (FACT-Cx) and MDASI.

QOL will be assessed using the Functional Assessment of Cancer Therapy-Cervix (FACT-Cx). The FACT-CX is comprised of 27-item general cancer concerns (FACT-G) and an additional 10-item cervical cancer specific scale. This summary score captures the FACT-G QOL dimensions of Physical, Functional, Social and Emotional Well-Being, plus the Cervical Cancer Subscale (7 items). Scoring will be done by the research personnel. The Trial Outcome Index is the sum of the Physical Well-Being (PWB), Functional Well-Being (FWB), and "additional concerns" subscales. The TOI is an efficient summary index of physical/functional outcomes. It is a common endpoint used in clinical trials, because it is responsive to change in physical/functional outcomes, sometimes more than a total (overall) multidimensional aggregated score which includes social and emotional well-being. While social and emotional well-being are very important to quality of life, they are not as likely to change as quickly or dramatically over-time or in response to therapy. The timing of the QOL and depression assessments will be administered after every two months [100, 101].

Symptom distress symptoms will be assessed by the MDASI, which assesses 13 common cancer-related symptoms, including pain, and six symptom-interference items, each rated over a 24-h recall period on a 0–10 scale. A composite interference score will be calculated as the mean of all six MDASI interference items for each patient [102, 103].

5.4.2 Demographics.

The patients' demographic characteristics will be collected before R/GI therapy and β-blockade. These include age, ethnicity, socioeconomic status, do-not-resuscitate status before and after enrollment, prior treatments, successive treatments, smoking status, baseline physical well-being (according to the TOI), and ECOG performance status.

5.4.3 The Brief Pain Inventory (BPI)

The BPI is a 9-item self-report instrument designed to assess pain in cancer and other diseases. The BPI has demonstrated reliability and validity across cultures and languages and has been used to study the effectiveness of pain treatment [104].

5.4.4 Experimental design: Translational Components

In this proposed study, we will have the benefit of obtaining blood specimens prior to and after administration of propranolol and will be able to generate preliminary data on the effects of propranolol on IL-6, IL-8, Il-10, CRP, Circulating HPV DNA and VEGF levels These data then can be correlated with biobehavioral measures that we will collect.

5.4.4.1 IL-6:

IL-6 expression is regulated by neural and endocrine responses to stress via feedback loops and by the hypothalamic-pituitary-adrenal axis at the pituitary and adrenal gland level [105, 106] IL-6 levels are elevated along with sympathetic activation (including cortisone and norepinephrine levels by acute and chronic stress and depression whereas IL-6 levels decrease following treatment of depression [83],[105] [107],[108],[109],[110],[111]. IL-6 is secreted by many cell types, including ovarian tumor cells, and is involved in many pathological processes in cancer patients. IL-6 stimulates proliferation of tumor cells [112, 113], enhances tumor-cell migration and attachment [113], promotes invasion of vascular endothelial cells by tumors [114] and angiogenesis [115], and is associated with tumor progression, shortened disease-free intervals, and poor OS [77, 116]. Oral cancer cells stressed by high levels of cortisol exhibit increased IL-6 expression and increased proliferation [111]. In melanoma cell lines, the presence of norepinephrine results in increased expression of VEGF, IL-8, and IL-6 [83]. In a study of patients with cervical dysplasia, IL-6 and IL-8 concentrations in cervicovaginal washings were higher in cervical carcinoma *in situ* (non-invasive dysplasia) patients than in normal controls and higher still in cervical cancer patients than in carcinoma

in situ patients [117]. Although relatively little data on IL-6 and cervical cancer are available, interestingly, stress hormones (norepinephrine and cortisol) can increase IL-6 mRNA production in oral squamous cell carcinoma cells, and this effect is blocked by treatment with propranolol. Researchers also have documented expression of β1- and β2-adrenergic receptors using polymerase chain reaction [111].

5.4.4.1.1 Methods:

IL-6 levels in plasma will be measured using enzyme-linked immunosorbent assays (ELISAs; R&D Systems, Minneapolis, MN), with results interpolated from using the standard curve provided with the ELISA kit. IL-6–expressing specimens with sensitivity below that of below the sensitivity cutoff for the regular assay will be quantitated using high-sensitivity ELISA (R&D Systems).

5.4.4.2 IL-10:

IL-10 is a counterregulatory or immunosuppressive mediator of stress-induced immunosuppression. IL-10 is extremely important to the initial transformation of cervical dysplasia to premalignant lesions. Investigators have shown that IL-10 expression is directly proportional to the development of HPV-induced cervical cancer [48]. Furthermore, in mouse models, stress-induced increases in IL-10 expression can be prevented by treatment with nadolol as well as a benzodiazepine [118]. Furthermore in a study of behavioral (telephone mediated) interventions, improvement in QOL seen in the intervention cohort was correlated with an inverse association between modulation of QOL and serum levels of IL-10 as indicated by the mean and standard error of the mean for a cohort of individual measurements [50].

5.4.4.2.1 Methods:

Serum levels of IL-10 (lower limit of detection, 0.5 pg/mL) will be measured in triplicate using standard ELISA (R&D Systems).

5.4.4.3 IL-8:

Chronic stress is associated with increase IL-8 levels [119]. IL-8 has a key role in regulation of angiogenesis, chemotaxis, and

enhancement of growth in a variety of tumors [120-122]. It is produced by tumor cells and macrophages [123]. In melanoma and ovarian cancer cell lines, treatment with norepinephrine has resulted in increased expression of VEGF, IL-8, and IL-6 [83, 119]. IL-8 contributes to the migration of tumor cells toward blood vessels and provides proliferative and antiapoptotic signals to tumor cells [124]. IL-8 overexpression is associated with advanced disease stage, high tumor grade, and decreased OS durations in cervical cancer patients [122]. IL-8 is thought to have an effect on tumor growth owing to expression of an angiogenic factor supplied by macrophages within and around cervical tumors. IL-8 expression has correlated with microvessel counts in cervical cancer patients [122], and microvessel density correlates with radioresistance and decreased OS duration [125]. Poorly oxygenated cervical tumors have increased microvessel densities, and this has correlated with decreased survival duration. Therefore, we hypothesize that IL-8 is a surrogate for angiogenesis changes that should be inhibited by the administration of propranolol.

5.4.4.3.1 Methods:

IL-8 expression in plasma will be measured using ELISA (R&D Systems), with the results interpolated from using the standard curve provided with the ELISA kit.

5.4.4.4 VEGF:

VEGF is one of the most potent proangiogenic molecules, inducing endothelial cells in vascular microvessels near tumors to proliferate and migrate and inducing alteration of their patterns of gene expression in favor of angiogenesis [126]. VEGF makes cells hyper-permeable, resulting in conditions favorable for angiogenesis in the extracellular matrix [127]. VEGF is produced by tumor cells, macrophages, and other cells. VEGF expression has been linked with norepinephrine stimulation of proliferation of cancer cell lines [83]. VEGF is critical to the growth and progression of cervical cancers and is a poor prognostic marker as consistent increases in VEGF expression are seen with increasing disease severity, and increased serum VEGF expression levels in other tumors are associated with metastatic disease and poor survival [98, 128, 129].

5.4.4.4.1 Methods:

Plasma VEGF expression will be measured using a standard ELISA kit (R&D Systems) (88). The minimum detectable serum level of VEGF = 5 pg/mL.

5.4.4.5 Circulating HPV

ctDNA can be detected in plasma of cervical cancer patients over stage I and HPV ctDNA concentration has been found to reflect tumor burden. In addition to its potential prognostic and predictive value, HPV mutation insertion is likely to constitute a new molecular surrogate of minimal residual disease and of subclinical relapse in HPV-associated tumor. This study will initially look at feasibility of obtaining this data in these patients with advanced recurrent cervical cancer [132, 133].

5.4.4.5.1 Methods

Plasma obtained from cervical cancer patients will be analyzed for HPV components in circulating cell-free DNA. DNA extraction will be performed using the Qiagen DNA extraction mini kit (Qiagen Biosciences, Germantown, MD). Quantification of target HPV genes (E2, E6, E7, L1 and L2) will be analyzed by Real-Time PCR using the Taqman Assay (Applied Biosystems, Foster City, CA). b-globin, GAPDH or b-actin will be used as a loading control. DNA concentration will be expressed as genome equivalents/per milliliter (GE/mL), as previously shown by our group (Kamat *et al*., 2006).

5.4.4.6 Indirect calorimeter (on patients accrued at MDACC)

Cachexia is not only associated with poor outcomes, but also with an unfavorable response to drug treatment and poor quality of life. It has been observed in patients with cancer that survival is impaired already at a weight loss of 5%; Weight loss exceeding 30% is incompatible with life. It is among the most common misconceptions that one of the underlying causes of cachexia is anorexia, i.e. loss of appetite. Although anorexia is certainly a common feature of the diseases leading to the development of cachexia, this feature alone cannot explain the metabolic changes observed during this perturbation. Importantly, nutritional supplementation cannot reverse the process of losing weight in patients with genuine cachexia, which is possible in patients who suffer from starvation or anorexia. Still, nutritional aspects have to be considered when treating patients with cachexia. Weight loss in the cachectic patient predominantly affects muscle protein,

however, bone and fat tissue are likewise affected later in the course of the disease [134]. The factors that trigger the progression from clinically and body weight stable, ambulatory CHF to cardiac cachexia remain poorly understood. The timelines differ widely between patients. We will aim to see effect of Beta Blockade on resting energy use.

Using the Indirect Calorimeter (manufactured by Microlife) each patient had their oxygen consumption (Vo_2) and carbon dioxide production (Vco_2) measured until recordings were in a steady state for 15–20 min. The total energy expenditure was calculated to determine the measured resting energy expenditure (MREE) under conditions of rest. The oxygen and carbon dioxide sensors were calibrated for accuracy before each measurement. Use of the indirect calorimeter takes roughly 15 minutes. Resting Energy Expenditure: Formulae for measuring resting energy expenditure (REE), such as the Harris-Benedict equation, may underestimate an individual's caloric requirements [135, 136]. A more accurate measurement of the REE can be made using indirect calorimeter. Each individual's REE measurement will take approximately 10-15 minutes using a handheld indirect calorimeter (MedGem 101, (MG); HealthTech, Golden, CO), at baseline (+/- 3 days) and at day 58 (+/- 3days). Measurements with the MG indirect calorimeter used single-use disposable mouthpieces and a noseclip for collection of expired air. Using the MG indirect calorimeter each patient has their oxygen consumption (Vo_2 (ml/min)) measured and REE (kcal/day). [2]

6.0 SAFETY PLAN AND CRITERIA FOR REMOVAL FROM STUDY

6. 1 Patient Safety

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria (see Section 3.2) and routine monitoring as follows:

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements (see Section 8.1). Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated approximately 30 days (28-42 days) after the decision to discontinue treatment.

6.2 Criteria for Removal from Study

6.2. 1 Patients will be removed from the study if they are unable to tolerate the lowest doses of the regimen because of toxicity.

6.2.2 Patients may withdraw from the study at any time for any reason.

7.0 TREATMENT MODIFICATIONS

Propranolol can be dose reduced if the patient's heart rate is less than 60 or systolic BP is less than 110 or diastolic less than 50 and showing symptoms at two different timepoints 24 hours apart. Also if the patient has side effects from the beta-blocker a dose reduction can be performed as outlined in Table E. All dose reductions will be made in the clinic. The maximum dose for propranolol should be 40mg po twice a day. For patients > 65 years old the maximum dose will be 20 mg by mouth twice a day. All dose adjustments will be made in the clinic.

Table E Modifications for Propranolol dosing

	Regimen -1 Level	**Regimen -2 Level**
Starting Dose 20 mg twice daily	**10 mg po bid (50%)**	**Discontinue**
Maximum Dose 40 mg twice daily	**30 mg po bid (25%)**	**20 mg po bid (50%)**

7.1 Hypotension.

Patients receiving propranolol should be monitored before each dose with measurement of blood pressure (see Section 5.0 Treatment Plan). If the SBP is less than 110 or the DBP is less than 50 and showing symptoms at two different timepoints 24 hours apart, the patient should be dose modified to regimen level -1 (see Table E). If after this dose modification there is still hypotension, then dose modify to regimen level -2 (see Table E). If patient still encounters hypotension, then discontinue the propranolol.

7.2 Bradycardia.

Patients receiving propranolol should be monitored with a measurement of heart rate. If the heart rate is less than 50 or 50-60 and showing symptoms at two different timepoints 24 hours apart, the patient should be dose modified to regimen level -1(see Table E). If after this dose modification there is still bradycardia, then dose modify to regimen level -2 (see Table E). If patient still encounters bradycardia, discontinue propranolol.

8.0 STUDY PARAMETERS AND SERIAL OBSERVATIONS

8.1 Observations and Tests

The following observations and tests are to be performed and recorded.

Observations and Tests	**Prior to Initial Study Treatment**	**On Treatment**			
		Month 1 (+/- 7 days)	Month 2 (+/- 7 days)	Month 4 (+/- 7 days)	End of Study (+/- 7 days)
History & Physical	1			4	
Blood Pressure	1	8	8	8	8
Heart Rate	1	8	8	8	8
Toxicity Assessment	1	8	4	4	4
CBC/Differential/Platelets	1		4	4	4
Serum Creatinine	1		4	4	4
Bilirubin, SGOT, SGPT, Alkaline Phosphatase	1		4	4	4
Magnesium	1		4	4	4
C-Reactive Protein (CRP)	1		4	4	4
PT/INR, PTT	1		5	5	
Serum Pregnancy test if childbearing potential exists	1				
EKG	1		6	6	
Indirect Calorimetry (MDA Pts. Only)	1		4	4	
Palliative Supportive Care	1		6	6	
QOL Surveys	3		7	7	
Demographic information	3				
Blood draw (TR)	3		7	7	
MRI, PET or PET/CT Scan of Chest/Abd/Pelvis	2		6		
Pill Diary		8	4	4	4
Relaxation Log		8	4	4	4

1. Must be obtained within 14 days prior to initiating propranolol therapy.
2. Must obtain CT, MRI or PET within 6 weeks prior to receiving any propranolol therapy.
3. QOL Surveys (MDASI, HADS, BPI, and FACT-Cx), demographic information and translational blood to be performed prior to initial study treatment
4. Must be obtained within +/- 7 days prior to clinic visit.
5. For patients on prophylactic or therapeutic anticoagulation with warfarin, PT/INR should be monitored before.
6. Only if clinically warranted.
7. Biobehavioral measures and QOL Surveys (MDASI, HADS, BPI, and FACT-Cx) are to be administered after completion of months 2 & 4 on trial and blood is to be drawn at clinic visit for translational purposes.

8. Blood Pressure and Heart Rate will be checked prior to starting propranolol in the clinic by research nurse/clinic nurse. At 48-72 hours after starting treatment, blood pressure monitoring needs to be done in the clinic by research nurse/clinic nurse but if patient unable to return to clinic, research personnel will contact patient for blood pressure readings. After that time, patient should continue to monitor blood pressure daily with their personal blood pressure machine, at their local pharmacy, or in the clinic. If personally monitoring their blood pressure, the patient should contact the research nurse if the SBP is less than 110, the DBP is less than 50 or heart rate 50-60 and showing symptoms at two different timepoints 24 hours apart.

9.0 EVALUATION CRITERIA

The present study is designed to evaluate the effect of β-adrenergic blockade and R/GI on advanced incurable cervical cancer.

We define this trial to be feasible if FACT Cx, BPI, HADS, and MDASI scores can be calculated for (1) all evaluable subjects at baseline, (2) 87% of subjects (13 out of 15) at Month 2, and (3) 73% of subjects (11 out of 15) at Month 4. Patients are considered nonevaluable if they leave the study through disease specific death or progressive disease prior to Month 4, and they will be replaced. Disease specific death does not include death due to excessive toxicity. All other patients are considered evaluable.

10.0 DURATION OF STUDY

Feasibility is determined by completion of three time points (TP0, 2, 4 mos). Patients who wish to continue on the regimen may do so until voluntary discontinuation, intolerability, disease progression, or death. The patient will be followed until death with assessment of medical notes in clinic station.

We will terminate the study early if too many patients experience dose-limiting toxicities (DLTs).

If removed from study, all patients will be weaned off the medication over the following 2 weeks. The dose will be reduced by 50% for 7 days then will be reduced to 25% of the dose for 7 days then discontinue completely. For patients that experience adverse effects during weaning the period of time can be increased as deemed appropriate.

11.0 STUDY MONITORING AND REPORTING PROCEDURES

A consent form must be signed by the patient prior to entry into study. Current Federal Drug Administration (FDA), National Cancer Institute (NCI) and institutional regulations concerning informed consent will be followed.

11.1 Reporting an Adverse Event.

11.1.1 An Adverse Event (AE) is any unfavorable and unintended sign (including abnormal lab finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

11.1.2 In the event of a serious adverse event (SAE) the first concern will be for the safety of the subject. Investigators are required to report to the Principal Investigator, who in turn must notify the IRB of any serious adverse events (SAE'S) that are possibly related to the study therapy, as per MDACC IRB guidelines.

11.1.3 An SAE is any sign, symptom or medical condition that emerges with propranolol treatment or during a post-treatment follow-up period that:

(1) was not present at the start of treatment and is not a chronic condition that is part of the patient's medical history, OR

(2) was present at the start of treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy.

AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

11.1.4 This study will utilize the Common Toxicity Criteria version 4.0 (CTC 4.0) for defining and grading specific adverse events.

Specific situations that require reporting to the IRB are summarized in the table below.

		Unrelated Unlikely	**Possible Probable Definite**
Grade 1	Unexpected & Expected	Not Required	Not Required
Grade 2	Unexpected	Not Required	7 Calendar days
	Expected	Not Required	Not Required
Grade 3	Unexpected with hospitalization	7 Calendar days	7 Calendar days

	Unexpected without hospitalization	Not Required	7 Calendar days
Grade 3	Expected with hospitalization	7 Calendar days	7 Calendar days
	Expected without hospitalization	Not Required	Not Required
Grade 4 & 5	Unexpected	24 hours	24 hours 3 Calendar days
Grade 4 & 5	Expected	24 hours	24 hours 7 Calendar days

1) "24 hours; 3 calendar days" - the investigator must initially report the AE within 24 hours of learning of the event followed by a complete report within 3 calendar days of the initial 24 hour report.

2) "7 calendar days" - a complete report on the AE must be submitted to the IRB within 7 calendar days of the investigator learning of the event.

11.1.5 Any medical event equivalent to a CTCAE grade 3, 4 or 5 that precipitates hospitalization must be reported regardless of attribution and designation as expected or unexpected with exception of any events identified as protocol-specific expedited adverse event reporting exclusions. This includes any grade 4 laboratory abnormalities that result in hospitalization.

11.1.6 Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported if the event occurs.

11.2 Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that propranolol, caused or contributed to an adverse event. The following general guidance may be used

11.2.1 *Yes:* if the temporal relationship of the clinical event to propranolol, administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

11.2.2 *No:* if the temporal relationship of the clinical event to propranolol, administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

11.3 Severe Adverse Event reporting:

11.3.1 The following events will require a **serious adverse event** report to be completed and reported to the Principal Investigator and the MD Anderson Cancer Center Institutional Review Board.

- Unanticipated side effect (not mentioned in consent, protocol or drug brochure)
- Event exceeds the nature, severity or frequency described in consent, protocol or drug brochure.
- Event involves a discrepancy between what was actually done to the research subject and what the subject was informed of when signing consent.
- Event requires discontinuation of study drug use.
- Event necessitates admission to hospital unless the hospitalization is anticipated due to the subject's disease or treatment.
- Event prolongs a stay in a health care facility.
- Event necessitates supportive treatment to prevent permanent impairment or damage.
- Event negatively affects prognosis.
- Event results in a new cancer.
- Event results in significant, persistent or permanent harm or disability***.**
- Event results in death.
- Any death within 30 days of receiving study drug.
- A congenital anomaly/birth defect.
- Event necessitates supportive treatment to prevent permanent impairment or damage.

***** Definition of disability: A substantial disruption of a person's ability to conduct normal life functions.

11.3.2 Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- **Life-threatening adverse drug experience:** Any adverse drug experience, including grade 4 laboratory abnormalities, that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

- **Unexpected adverse drug experience:** Any adverse drug experience, the specificity or severity of which is not consistent

with the current Investigator Brochure; or if an Investigator Brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

- **"Unexpected"**, as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., is not included in the Investigator Brochure) rather than an experience that is not anticipated based on the pharmacological properties of the pharmaceutical product.

12.0 STATISTICAL CONSIDERATIONS:

This is a feasibility study. Feasibility is defined in terms of patient enrollment, completion of survey scales, and safety of beta-blocker regiment. Specifically, we will consider this trial feasible if:

1. on average, we enroll at least 1-2 patients each month.

2. FACT-Cx, BPI, HADS, and MDASI scores can be calculated for (1) all evaluable subjects at baseline, (2) 87% of subjects (13 out of 15) at Month 2, and (3) 73% of subjects (11 out of 15) at Month 4; and

3. $\Pr(\pi_t \leq 0.2 \mid \text{data}) > 90\%$ where π_t is the proportion of any grade 3-4 toxicities that are probably, possibly, or definitely related to the intervention.

Scores for the FACT-Cx can be calculated when at least 50% of the items on each subscale have been answered. A total score for the FACT-Cx can be calculated when at least 80% of the total items have been answered and each subscale has a score.

Scores for BPI: Pain Severity can only be calculated when all 4 items have been answered. Scores for BPI: Pain Interference can be calculated when at least 4 out of the 7 items have been completed.

Scores for HADS: Anxiety can be calculated when at least 6 of the 7 anxiety items have been completed. Likewise, scores for HADS: Depression can be calculated when at least 6 of the 7 depression items have been answered.

Scores for MDASI: Symptom Severity can be calculated when at least 7 of the 13 items have been completed. Scores for MDASI: Symptom Interference can be calculated when at least 4 of the 6 items have been completed.

Patients are considered nonevaluable if they leave the study through disease-specific death or progressive disease prior to Month 4, and they will not be replaced. Disease-specific death does not include death due to excessive toxicity. All other patients are considered evaluable. In addition to calculating the percent of women who complete these quality of

life (QoL) measures, we will calculate the percent of women completing combined intervention of twice daily beta blocker and twice weekly progressive muscle relaxation and guided imagery at Month 2 and Month 4.

The secondary objectives of this study are to estimate the impact of beta blocker and relaxation intervention on symptoms, anxiety, depression, pain and QoL. We will examine symptoms and symptom distress using the MDASI, anxiety and depression using HADS, pain using the BPI and QoL using the Trial Outcome Index (TOI) of the FACT-Cx.

The exploratory objectives of this study are to measure changes in serum levels of IL-6, IL-8, IL-10, VEGF, CRP, and resting energy use via calorimeter, as well as to measure HPV components (e.g. E6 and E7) in circulating cell-free DNA.

All secondary and exploratory endpoints will be examined graphically and through summary statistics. Ninety percent confidence intervals will be calculated for all endpoints, including feasibility endpoints.

We will recruit 20 patients to obtain 15 evaluable patients. With 15 subjects, if we have data for 87% of the women at Month 2 and 73% of the women at Month 4, our exact 90% confidence intervals at Months 2 and Months 4 will extend from 64% to 98% at Month 2 and 49% - 90% at Month 4. Additionally, with 15 subjects, the boundaries of our 90% confidence interval for sample means will extend 0.43 standard deviations on either side of the sample mean. We will also track number of patients approached and, if appropriate, reasons for declining to participate.

13.0 DATA MANAGEMENT

13.1 Registration

13.1.1 When a patient is found to be eligible for study, a signed informed consent will be required by the managing physician.

13.1.2 Questions concerning eligibility may be addressed to the Study Chair(s), Contact Person/Data Manager or Nurse Contact. A protocol number will be assigned.

13.1.3 All patient entries will be registered in CORe. The following forms will be completed in a timely fashion and will be placed in the subject's study chart. (Appendices D-G and I-T).

14.0 TRANSLATIONAL RESEARCH (See Appendices H and I)

14. 1 Specimen Collection

Blood Draws:

An approximately 28 mL (5-6 tsp) blood sample (2 green tops, 1 CPT tube) will be obtained at time of enrollment prior to the initiation of propranolol. All blood will be immediately processed and frozen in at least 5 aliquots at –80º C. The plasma will be used to perform ELISA assays for VEGF, IL-6, IL-8., and circulating HPV.

14.2 Specimen handling:

Plasma for detecting of cytokines and angiogenic markers: 20 ml (4-5 tsp) of whole venous blood is collected in two **greentop tubes**. The tubes of whole blood should be allowed to sit for 10 minutes or until clotting is complete. Centrifuge the tube at 3000 rpm for 10 minutes. Transfer the plasma using a transfer pipet. Store the plasma in polypropylene cryostorage tubes. Aliquot .2 ml per tube. Freeze within 2 hrs of phlebotomy.

14. 3 Types of Laboratory assays:

Multiplex ELISA for detecting IL-6, IL-8, VEGF. Multiplex ELISA will be carried out based on the manufacturer's instruction for detecting both human and mouse IL-6, IL-8, VEGF, in plasma collected at the visit prior to starting therapy, at the 2^{nd} mos of treatment and the 4^{th} month of treatment Coupled with the Luminex xMAP®platform in a magnetic bead format, the MILLIPLEX® MAG Human Cytokine / Chemokine panel (Millipore Corporation, Billerica, MA) allows us to quantitative multiplex detection of dozens of analytes simultaneously, which can dramatically improve productivity.

Microarray will be performed at Genomics Core Facility. RNA will be isolated from PBMCs using MirVana RNA extraction. RNA extracted from patients before and after treatment will be sent to Core Facility for microarray analysis.

14.4 Shipping:

Contact Zhiefi Zu for sample processing. All blood samples will be batched shipped to Dr. Anil Sood's laboratory at M.D. Anderson Cancer Center in Houston, Texas. All samples will be de-identified by a number that is only recognizable by the Principal Investigator.

15.0 PROTOCOL COMPLIANCE

The attending physician and oncology nurse must see each patient prior to each study time point indicated. All required interim and pre-treatment data should be available to the physician. The physician must make a toxicity grade. All study parameters required by protocol before each cycle of therapy must be documented.

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