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Can Advances in Immunotherapy Improve the Survival in Women with Recurrent Cervical Cancer?

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Short Communication

Cervical cancer is the second leading cause of female cancer related deaths in the world with an estimated 266,000 lives lost each year [1,2]. An estimated 2.27 million women worldwide have cervical cancer at any given moment in time and approximately 528,000 new women are diagnosed each year worldwide [2]. The brunt of the diagnosis, a staggering 80%, occurs in developing countries [2]. Due to advances in screening techniques and public awareness, the overall rate of cervical cancer in the United States has declined. However there are still approximately 12,500 new, cases of cervical cancer diagnosed each year and 4,100 women die from their disease each year [3]. Additionally, it is estimated that over 300,000 women in the United States have a diagnosis of CIN 2/3, the precursor to cervical cancer [4].

The Human Papilloma Virus (HPV) is the oncogene virus responsible for the development of cervical dysplasia and progression to cancer. HPV is small double stranded DNA virus and infection leads to a loss of cell cycle regulation and a resistance to apoptosis [5,6]. This causes increased genetic instability and cell proliferation. Tumor suppressor proteins are then sequestered and the HPV virus is integrated in the cellular DNA. This leads to up regulation of viral oncogenes and increased chromosomal abnormalities with activation of telomerases [7]. E6 and E7 are the oncogenes that bind p53 and retinoblastoma proteins to facilitate inhibition of tumor suppression of the 12 high-risk subtypes, 16, 18 are responsible for 70% of all cervix cancer [5].

Primary disease

Unlike most of gynecological cancers that require surgical staging, cervical cancer remains a clinically staged disease, wherein CT or PET imaging findings do not influence the stage. Primary treatment either involves surgery for early stage and chemo radiation for advanced stage cervix cancer [8]. Stage 1A1 cancers can be managed with either cold knife cone in the event fertility is desired or simple hysterectomy whereas stages 1A2 to 1B1 are mostly managed with a modified radical hysterectomy and a pelvic node dissection. Occasionally, IA2 to IB1 can also be managed with radical trachelectomy when fertility is desired in select women with small tumors less than 2cm and absence of Lympho Vascular Space Invasion (LVSI). Most stage 1B2 and above are treated with cisplatin based chemo radiation. Five year survival is estimated between 80-93% for stage I, 58-63% for stage II, 32-25% for stage III and 15-16% for stage IV [9].

A look at the probability of surviving recurrence-free in advanced stage cancer for at least 3 years is discouraging. The estimated survival probabilities are 69%, 33%, 56% and 10% for subjects with stage 2B, 3A, 3B and 4A disease respectively [10]. Additionally women with early clinical stage and positive lymph nodes also prognostically do poorly. Ina study with subjects with advanced cervical cancer who are surgically staged and then treated with radiotherapy, 5-year PFS was 57% for node-negative subjects but decreased to 34% and 12% for subjects with pelvic and para-aortic lymph node metastases, respectively [11]. The four-year risk of death and recurrence for these node positive women and patients with advanced stage cervix cancer is 50% [11]. These statistics are staggering and highlight the need of better treatment options for these patients for both prevention and treatment of recurrent disease.

Recurrent disease

In 2011 Duenas-Gonzalez et al. reported a 9% improvement in PFS by adding concurrent gemcitabine to weekly cisplatin during radiation followed by 2 additional cycles of cisplatin-gemcitabine [12]. Unfortunately, there remains a high rate of recurrence following primary treatment and currently there are limited treatments available for recurrent disease. This unmet need is highlighted by the fact that there are actually only three single agent chemotherapy regimens that

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are FDA approved for treatment of recurrent cervical cancer which are Bleomycin, Topotecan and Bevacizumabin last 50 years, with cisplatin-gemcitabine being the only approved combination [13]. From 1998 through 2015, there were greater than 20 Phase 2 studies involving persistent or recurrent metastatic cervical cancer conducted by the Gynecologic Oncology Group (GOG). Until recently, only one study had met the predefined efficacy and safety threshold to progress to second stage of enrollment. Monk et al. found that Bevacizumab demonstrated a median OS of 7.3 months and at 12-months OS was equal to 30% [14]. Then in 2014, results from GOG 240 demonstrated that addition of bevacizumab to single agent chemotherapy compared to single agent therapy aloneimproved OS with median OS of 16.8 months compared to 13.3 months in recurrent disease [HR=0.765 (95% CI, 0.62-0.95) p=0.0068] [15]. While this was a significant gain in meaningful OS, there remains an enormous need for new novel therapies that can provide meaningful progression free periods and improve overall survival for patients with advanced or recurrent cervical cancer.

Novel therapies on the horizon

One of the promising new therapies that could change the course of persistent or recurrent cervical cancer is immunotherapy, leveraging a patient's own immune system to fight cancer. It is an attractive strategy for cervical cancers because these tumors nearly universally harbor the HPV E6 and E7 antigens. E6 and E7 are appealing therapeutic targets because they are constitutively expressed, tumor specific, and functionally important, and they can be recognized and attacked by the human adaptive immune system. Currently, there are four classes of immunotherapy treatments; adoptive T cell therapy, monoclonal antibodies, checkpoint inhibitors and vaccines.

Adoptive T-cell therapy

T-cell therapy is utilized by removing a patient's T-cells, genetically modifying them and then reintroducing them into the patient with the goal of improving T-cell recognition and anti-cancer response. In a provocative study by Hinrichs et al, patients with a diagnosis of metastatic cervical cancer and previous platinum based chemotherapy or chemo radiation had surgically harvested tumor infiltrating lymphocytes [16]. The patients then underwent lymphocyte-depleting chemotherapy, augmentation with IL2 and then were treated with a single infusion of "tumor-infiltrating T-cells" (TILs) that had been selected for HPV E6 and E7 [16] reactivity. Three out of nine patients experienced objective tumor responses, two with complete responses and the other with a partial response [16]. The two complete responses were ongoing 22 and 15 months after treatment, respectively with a partial response of 3 months. The HPV reactivity of T-cells in the infusion product as measured by interferon gamma production, enzyme linked immune spot and CD137 up regulation assays correlated positively with clinical response (p=0.0238 for all three assays) [16]. Additionally, the frequency of HPV reactive T-cells in the peripheral blood 1 month after treatment was positively associated with clinical response (p=0.0238) [16]. Similar phase 2 trials are now currently underway time for TILs therapy.

Monoclonal antibodies

Antibodies are proteins that fight infection and our body produces them when it detects a toxin or foreign substance known as an antigen. Monoclonal antibodies are made in a laboratory and designed to attack a specific cancer protein and in immunotherapy, they are designed to attach itself to a specific cancer protein that would enable the immune system to recognize the cancer cell and attack it. Currently ongoing trials with available monoclonal antibodies with activity directed at cervical cancers include HuMax®-TF-ADC, an antibody drug conjugate targeting tissue factor-specific cells and are being tested in two clinical trials in patients with advanced cancer including cervical cancer (NCT02001623, NCT02552121). Additionally, IMMU-132, (TisotumabVedotin) is an antibody drug conjugate targeting the TROP-2 antigen, which is expressed in a variety of cancers, and is being tested in a phase I/II trial in patients with advanced cancer, including cervical cancer (NCT01631552).

Immune checkpoint inhibitors

Immune checkpoint inhibitors work by targeting molecules which serve as the "checks and balances" in the regulation of T-cells or those molecules which inhibit T-cells and prevent them attacking native cells [17]. The checkpoint is a protein on the cell that signals the T-cells not to attack. A checkpoint inhibitor is designed to remove this mechanism from cancer cells thereby allowing the T-cells to identify and attack them. Preliminary results from the phase II KEYNOTE-158 study using pembrolizumab , a humanized antibody that targets PD L1 receptor demonstrate, among patients with recurrent or metastatic cervical cancer a overall response rate of 11%, and another 30% of patients had stable disease [18]. 87% of patients had PD1expression on immune histochemistry, 52% of patients had 2 or more prior lines of therapy [18]. The median time to their noted response was 2.1 months (range 1.6 to 4.2 months) and 100% of the 10 responding patients had not had disease progression for a time range 4.2 to 8.7 months [18]. The drug is well tolerated and the study is ongoing but holds promise that for a subset of patients with PD-L1 positive tumors.

GOG 9929 is a completed phase 1 study that showed the safety of using Ipilimumab, a monoclonal antibody that activates the immune system by targeting CTLA-4, a protein receptor that down regulates the immune system, in patients with early cervix cancer and positive nodes or with advanced disease as a consolidation strategy to reduce recurrence rates [19].

Vaccine therapy

Vaccine therapy for prevention of cervix cancer had now become main stream, with increasing rates of vaccination all across the US. These include 3 FDA approved HPV vaccines; Gardasil, Gardasil 9 and Cervarix, all of which have remarkable efficacy and safety data in preventing cervix and other HPV related cancer such as vulva, vagina and anal cancer [4]. They are currently approved for administration from age 9 years until 26 years [4]. A breakthrough in the development of HPV vaccines was the observation that the major capsid protein (or the L1 protein) could self-assemble into noninfectious virus-like particles [20]. Virus-like particles closely resemble live virus morphologically and can induce high titers of antibodies against live HPV types. VLPs are nontoxic, immunogenic and possess no oncogenic potential. Several phase II trials using various types of HPV vaccines have been completed and presently, several phase III HPV vaccine trials are underway.

One therapeutic vaccine that has shown promise in phase I-II trials is the vaccine ADXS11-01 (axali-mogene filolisbac). It is a vaccine that consists of live attenuated Listeria monocytogenes that has been modified to secrete an HPV16-E7 fusion protein. When this is recognized, T helper cell immunity is triggered and cytotoxic T cells are recruited to target the HPV-E7 cells in the tumor. Additionally, it simultaneously suppresses the immunologic defenses within the lesions, by decreasing T reg and MDSC's in the

tumor microenvironment [21]. In a phase II study of Indian women with recurrent cervical cancer randomized to receive ADXS11-01for 3 doses with or without concurrent cisplatin, Petit et. al found that 12-month OS was 32% with a RR of 11%and disease control rate of 38% [21]. Additionally, cisplatin improved toxicity but did not improve survival or tumor response.

This data was confirmed by a subsequent trial GOG 265, that enrolled 46 patients in a 2 step phase II trial in women with recurrent, previously treated cervical cancer [22].52% of all patients had 2 or more prior lines of therapy, 56 % had prior bevacuzimab and 86 % had prior radiation therapy. The 12 month OS was 38 %, the highest OS seen over 20 years of phase II trials in cervical cancer by the GOG in second line setting, where the average survival is 4-7 months [14]. The clinical benefit was seen in 32% of patients with one complete response which is ongoing for over 24 months. The vaccine was generally well tolerated with a 10% of patients experiencing a grade 3 Cytokine Release Syndrome (CRS) [22].

There is a phase III trial in the process of being launched, with the vaccine combination with a PDL1 targeting checkpoint inhibitor. The vaccine is also available in a large phase 3 trial in a consolidation setting to prevent recurrence in patients with advanced cervix cancer after chemo radiation. This study is a double blind placebo controlled randomized trial that randomizes patients 1:2 to receive the placebo or the ADXS11-001 vaccine for a year and is currently accruing patients.

Conclusion

In conclusion, while great strides have been made in improving screening and prevention for cervical cancer, the recurrence rates for node positive early and locally advanced cervical cancer remains unacceptably high [11]. Additionally, treatment options currently available for patients diagnosed with recurrent disease are limited in efficacy. While many studies are underway in recurrent cervical cancer, immunotherapy is an area that holds promise to turn the tide in the treatment of this disease.

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