Report on Three Cases of Advance Ovarian Cancer Upon Bangladeshi Population: Successful Management with Bevacizumab Based Chemotherapy

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ABSTRACT

Ovarian cancer is an alarming health problem in Bangladesh. The annual mortality rate per 100,000 people from ovarian cancer in Bangladesh has increased by 40.3% since 1990, an average of 1.8% a year. Globcan predicts a change in the reported incidence of ovarian cancer from 2912 in year 2012 to 3132 in 2015. Recurrent high-grade ovarian cancer is usually associated with short term survival. There are few guidelines to surgically and medically treat long term survivors with ovarian cancer. We are reporting three cases on advance ovarian cancer patients; all are married, age ranging from 40-60 years, primarily treated with chemotherapy. After that, they were experienced with FDA approved (Nov 14, 2014) monoclonal antibody Bevacizumab (AVASTIN), additionally with chemotherapy.

Key Words: Advance ovarian cancer, Chemotherapy, Bevacizumab, Recurrent.

Introduction

Ovarian cancer is a cancer that forms in an ovary[3]. It results in abnormal cells that have the ability to invade or spread to other parts of the body[4]. When this process begins, there may be no or only vague symptoms. Symptoms become more noticeable as the cancer progresses[5,6]. These symptoms may include bloating, pelvic pain, abdominal swelling, and loss of appetite, among others[5]. Common areas to which the cancer may spread include the lining of the abdomen, lining of the bowel and bladder, lymph nodes, lung, and liver[7,8]. The risk of ovarian cancer increases in women who have ovulated more over their lifetime. This includes those who have never had children, those who begin ovulation at a younger age or reach menopause at an older age[9]. Other risk factors include hormone therapy after menopause, fertility medication, and obesity[3]. About 10% of cases are related to inherited genetic risk; women with mutations in the genes BRCA1 or BRCA2 have about a 50% chance of developing the disease. The most common type of ovarian cancer, comprising more than 95% of cases, is ovarian carcinoma[9]. Screening is not recommended in women who are at average risk, as evidence does not support a reduction in death and the high rate of false positive tests may lead to unneeded surgery, which is accompanied by its own risks[10]. Those at very high risk may have their ovaries removed as a preventive measure[5]. If caught and treated in an early stage, ovarian cancer may be curable. Treatment usually includes some combination of surgery, Targeted therapy, radiation therapy, and chemotherapy[5]. Outcomes depend on the extent of the disease and the subtype of the cancer present[9]. The overall five-year survival rate in the United States is 45%[11]. Outcomes are worse in the developing world[9].

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However, trials of the antibody and VEGF inhibitor bevacizumab, which can slow the growth of new blood vessels in the cancer, have shown promising results[12]. Bevacizumab has been particularly effective in preliminary studies on stage-III and -IV cancer, Bevacizumab can also be combined with platinum chemotherapy, a combination that has had positive preliminary results in PFS, but equivocal results regarding overall survival[12].

Case 1

Mrs. X, 62 years muslim lady, normotensive, non-diabetic, non-asthmatic patient hailing from Dhanmondi, Dhaka. In December 2007, the patient had come with one week history of abdominal distension which was progressive in nature. She was investigated and revealed a raised CA125:950, abdominal tap was positive for malignant cells. U/S abdomen revealed right pleural effusion and moderate ascites.

Patient underwent U/S ovary in SGH: uterus was not enlarged. No uterine masses seen. The ovaries were ill defined. Collection of echos seen in right adnexum. This may represent a loop of intestine although an ovarian lesion cannot be excluded. It measures approximately 33mm x27mm in size. Fluid was present in abdominal and pelvic cavities and in the lung bases. OGD and colonoscopy done for her were normal. Patient underwent ultrasound guided ascetic fluid aspiration, the fluid was then sent for further investigations. Concentration of CA125 was raised to 991. Histology of peritoneal fluid: metastatic adenocarcinoma. Immuno profile: The tumor cells were CK7 positive, calretinin negative, CD1125 focally positive, CDX2 negative. The above findings were in favor of metastatic ovarian carcinoma or peritoneal disease.

Patient underwent abdominal tap and a total of 2.5 liters was drained. Patient was admitted electively for chemotherapy. Planned for 3 cycles of taxol+carboplatin before planning for primary debulking surgery.

After that, from 1st to 6th cycle she got Taxol+Carboplatin followed by THBSO and omentectomy, appendicetomy (histopathologically complete remission). Subsequently disease was progressed in 2009 and she received Carboplatin+Gemzar+Avastin (Bevacizumab) at her 13th cycle of chemotherapy. From 7th to 12th cycle she got Carboplatin + Doxorubicin with acceptable toxicity profile. She was noted to have noted right hypochondrial pain in Aug 2012 with CT PET: Disease recurrence at liver. She thus came to seek review. She had performed an MRI liver which revealed mainly perihepatic and peritoneal disease, no liver parenchymal disease seen. Option of palliative chemotherapy was discussed with patient and her family.

In 2011, she had taken total 6 cycle of chemotherapy (13th to 18th). She received Carboplatin+Avastin+Taxol/Gemzar/Taxotare in different stages of her chemotherapy cycle from 19th to 24th in 2012. In 2013, She had been started her 25th cycle with only Avastin (500mg). She received Neulastim (1amp) additionally with chemotherapy in her 28th cycle, because of neutropenia. She has taken her last chemotherapy on Jan 09, 2017. It was her 47th cycle. She is continuing her treatment, Though she is a patient of aggressive Advance Ovarian Cancer (stage 4), her disease progression is successfully managed by her current treatment protocol.

Case 2

Ms. Tahera, 37 years old, regularly menstruating, got admitted to UHL under Obs & Gynae dept on 28.06.2009 with the complaints of swelling of a abdomen for 2 months and vague abdominal discomfort, bloating and weight loss for 6 months. She is normotensive, nondiabetic. P/A/E reveals a large solid mass about 16x18 cm occupying umbilical, hypogastic & left & right lumber region. Investigations revealed Hb: 9.3 gm/dl, CA-125: 207.88 U/ml, betah CG: 102.71 Miu/ml. CT Scan showed bilateral ovarian neoplasm. Probably malignant with abdominal lymphadenopathy bilateral hydronephrosis and hydroureter. Her total hysterectomy with bilateral salphingo-opherectomy with infracolic omentectomy were done on 30.06.2009. Histopathology showed clear cell Adenocarcinoma of ovary. Both peritoneal fluid and omentum were also positive for malignancy. The patient was transferred to oncology dept. for further

treatment on 12.07.2009. She was given 6 cycle of chemotherapy of carboplatin 350 mg DI, paclitaxel 240 mg DI and six cycles of Targeted therapy Bevacizumab (Avastin) 400 mg dose treatment and it was non-event full. In the meantime her CBC, LFT, RFT CEA, CA125 was normal. The patients were then evaluated by PET-CT scan in Singapore and FBG positive pelvic node was identified. Patients was then given option for second look surgery but patients party refused surgery and agreed to Receive Further chemotherapy and targeted therapy. Then she was given 3 cycle of second line, Avastin, Gemcitabine & Oxaloplatin. Review MRI was done and showed no change in abdominal (Lymphoid) lesion. But CA-125 is in good control and patients are Asymptomatic. Latest CA-125 result is 2.56U/ml (19.02.2014). In 2016(18.03.2016) whole body FDG PET-CT scan was done. Now patients come follow-up 6 monthly & patients iaAsymptomatic.

Case 3

Patients Age 45. Post menopausal, nondiabetic HTN presented with sudden respiratory dissension, abdominal discomfort and ascites. She was investigated and revealed a raised CA-125.

CT. Scan shows lung metastasis and mass in right ovary. Emergency CT guided aspiration was done. Exploratory laparotomy & total abdominal hysterectomy with bilateral salpingo-ophorectomy were done. Histopathology showed cysts adenocarcinoma with positive ascetic fluid for malignant cell. Her CA-125 was 5000. She was diagnosed as a stage 4 ovarian cancer.

Then she received adjuvant chemotherapy 6 cycles with the targeted therapy bevacizumab (Avastin). Her CA-125 cancer marker returned to normal. After 12 months later her CA-125 level rises and then again received 6 cycle of paclitaxel, gemcitibine, cisplatin and targeted therapy bevacizumab (Avastin).

She received 6 cycle adjuvant chemotherapy like carboplatin plus paclitaxel and targeted therapy Bevacizumab (Avastin). Every three months she comes to the chamber for follow-up and patients is asymptomatic.

Discussion

Globally, as of 2010, about 160,000 people died from ovarian cancer, up from 113,000 in 1990[14]. As of 2014, more than 220,000 diagnoses of epithelial ovarian cancer were made yearly[15]. Ovarian cancer is most commonly diagnosed after menopause[15], between the ages of 60 and 64. 90% of ovarian cancer occurs in women over the age of 45 and 80% in women over 50[16].The annual mortality rate per 100,000 people from ovarian cancer in Bangladesh has increased by 40.3% since 1990, an average of 1.8% a year. Though this has been the trend overall, adjust the filters at the top of the visualization to see how the mortality rate for ovarian cancer has changed over time for women of specific age groups in Bangladesh[17].

Cancer is one of the leading causes of morbidity and mortality in Bangladesh. The estimated cancer load is 1.2 million with an incidence of 2000000, a prevalence of 800000 and mortality at 150000. Cancer incidence is expected to double in the next 20 years[18]. In a survey of 117 cancer patients in Dhaka, 8.1% had ovarian cancer[19].

We report the case of women with advanced and high-grade epithelial ovarian cancer who survived for 10 years despite recurrences. They received complex and highly sophisticated oncologic care in Bangladesh. While the mean five-year overall survival from advanced epithelial ovarian cancer is 20%. There is a subset of women who are long-term survivors.

In a review of 251 women with advanced stage ovarian cancer univariate analysis revealed that FIGO stage 3 and stage 4, elevated CA125, and suboptimal de bulking were significant in reducing duration of progression free survival(PFS) and overall survival (OS).

One of the challenges for cancer patients in Bangladesh is the tremendous cost of care. Women with ovarian cancer consume a large proportion of healthcare resources[20]. Bangladesh has developed a pluralistic healthcare system, which includes government services, multiple NGOs and robust private sector[21]. Majority of Bangladeshi citizens cannot afford healthcare and do not have access to

complex care our patients received[22]. Development of universal healthcare insurance must be part of the strategy in Bangladesh for complex care such as ovarian cancer[23,20].

Prognosis is not good in advance stage of ovarian cancer. Treatment options in recurrence metastasis stage is limited for ovarian carcinoma. So conventional treatment regimen show poor response and survival. So newer molecule need to investigate that enhance the efficacy ovarian carcinoma in advance stage[24].

Vascular endothelial growth factor (VEGF) and angiogenesis are important promoter of ovarian cancer progression[25,26]. Both co-relate directly with the extent of disease and inversely with progression free survival[27,28] and overall survival[29,30,31] often in dependently of known prognostic factors[32,33].

Bevacizumab, a humanize VEGF-neutralizing monoclonal antibody, inhibits tumor angiogenesis[4]. We investigate the integration of bevacizumab with our conventional treatment protocol.

In the first case- The patients was 62 yrs. old and first she diagnosed ovarian cancer at 2007. Sequentially she taken conventional chemotherapy and targeted therapy bevacizumab. At 10 years later she comes to dr. chamber regularly and she continued the single agent bevacizumab.

In case 2 & 3 another two patients they also diagnosed stage 4 ovarian cancer. They also get all the standard treatment and they come to the chamber 3 months intervals

In our finding from three case studies, bevacizumab is one of the important monoclonal antibody showed single agent activity in woman with recurrent ovarian cancer.

Conflict of interest: We have no conflict of interest.

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