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CASE REPORT

Diagnosis and Management of Ovarian Cancer: Current Status and Future Potential

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ABSTRACT

Ovarian carcinoma is the fifth common cause of cancer death among women in Malaysia, with five-year survival rates of 30%. It has been associated with delayed diagnosis, advanced stage of presentation and poor prognosis due to vague symptoms and lack of effective screening. The continued high fatality rate has underpinned efforts to develop effective screening tests and newer therapies that could impact on prognosis. New insights into proteomic analysis and genomic tests with a better understanding of the target lesion have leading to discovery of new treatment modalities in ovarian carcinoma. We present a 58-year-old lady with Stage IV ovarian cancer who had lower abdominal pain and mass, constipation and voiding frequency for six months duration. Ultrasound guided biopsy revealed serous adenocarcinoma likely ovarian in origin. CT scan showed gross ascites and right ovarian mass with infiltration to adjacent small bowel. Tumour markers CA 125 and LDH were high. She has received neoadjuvant chemotherapy followed by cytoreductive surgery and currently in remission.

INTRODUCTION

Ovarian cancer is the commonest cause of gynaecological-cancer associated death, which often presents in postmenopausal women. Most women have advanced disease presenting with abdominal pain and distension, for which primary debulking surgery and platinum-based cytotoxic chemotherapy has been considered the cornerstone of treatment[1]. Vague symptoms

and advanced stage of presentation have led to discovery of proteomic analysis that can identify biomarkers for early detection of ovarian carcinoma. The different treatment modalities include tyrosine kinase inhibitors, PARP inhibitors, ONX-0801, genetic therapies, and mirvetuximab soravtansine. This case highlighted the importance of proteomic analysis and genomic tests, and new therapies for ovarian carcinoma.

CASE PRESENTATION

A 58-year-old lady was admitted for operation for ovarian carcinoma diagnosed 5 months prior to current admission. Six months earlier, she presented with on-and-off lower abdominal pain with noticeable mass that progressively increased in size. She had symptoms of constipation and voiding frequency. At the same time, she was complaining of abdominal distension and vomiting food particles after eating. Other complaints include fatigue, loss of appetite and significant loss of weight. Otherwise, she had no significant past medical, family or social history.

One month after occurrence of these symptoms, she went to a general hospital, where she was found to have ascites. Peritoneal tapping revealed atypia suspicious of malignancy, ultrasound guided biopsy revealed serous adenocarcinoma likely ovarian in origin whereas CT scan showed gross ascites and right ovarian mass measured 6.8 × 7.2 × 7.7cm, with infiltration to adjacent small bowel. Tumour markers were done and the results were CA 125 (983.4 U/mL), AFP (0.963 ng/mL), CEA (4.04 ng/mL), β-hCG (<5 mIU/mL) and LDH (589.4 U/L), CA 125 and LDH were high, CEA was low while AFP and β-hCG were normal. Hence, she was given the diagnosis of advanced right ovarian carcinoma. One month later, she developed right moderate pleural effusion shown on CT thorax.

Subsequently, she was started on 4 cycles of neoadjuvant carboplatin and paclitaxel, while CT scan and tumour markers were used to monitor her status. Right pleural effusion and ascites had resolved, size of right ovarian mass also reduced to 3.1 × 3.2 × 3.8cm after fourth chemotherapy whereas CA 125 level was 26.1U/mL after fourth chemotherapy. She was then planned for hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic node dissection, appendicectomy and debulking. However, surgery could not proceed as she developed lung infection. Chemotherapy was continued, which is 8 cycles in total. Patient has completed her 8th cycle of chemotherapy followed by surgical debulking, and she is currently in remission.

DISCUSSION

Historically, primary debulking surgery has been considered the cornerstone of treatment for patients with advanced epithelial ovarian carcinoma. However, there has been a paradigm shift in the philosophy of primary management after the study by the European Organization for Research and Treatment of Cancer (EORTC) – National Cancer Institute of Canada (NCIC) randomised trial of primary cytoreductive surgery followed by platinum-based chemotherapy versus three cycles of platinum-based neoadjuvant chemotherapy (NACT) followed by an interval debulking operation (if there was no disease progression) for patients with stages IIIC or IV ovarian, fallopian tube or primary peritoneal carcinoma[2] and the CHORUS study done in the United Kingdom and New Zealand[3] which demonstrated comparable survival in patients having primary debulking surgery or NACT, but with less morbidity and mortality in those having neoadjuvant chemotherapy. Survival was best if there was no residual disease following operation. NACT should be considered in patients whose postoperative morbidity and mortality can be significantly reduced including those with gross ascites or pleural

effusion, on the basis of poor nutritional or performance status, in which they will be much fitter to have radical surgery and better to cope with it psychologically[4]. Otherwise, primary debulking surgery should be the option as neoadjuvant chemotherapy is associated with increased difficulty during surgery by creating inflammatory adhesions and increased risk of inducing platinum resistance, with no improvements in prognosis[5]. Neoadjuvant chemotherapy does not compromise the survival of women treated for advanced ovarian cancer. Prospective randomized trials comparing neoadjuvant chemotherapy to conventional therapy to determine quality of life experiences and cost/benefit outcomes are now appropriate for women presenting with advanced ovarian cancer[6].

Proteomic analysis identifies biomarkers that can detect early stage of ovarian cancer, by distinguishing serum protein pattern signatures of ovarian cancer in patients with early- and late-stage disease using mass spectroscopy with bioinformatics. Retinol binding protein 4 (RBP4) is a potential biomarker in a study by Yu Shan et al. [7] while apolipoprotein A1, a truncated form of transthyretin and a cleavage fragment of inter--trypsin inhibitor heavy chain H4 are biomarkers identified in the study by Zhen et al.[8], with sensitivity to detect early stage ovarian cancer using a multivariate model combining the three biomarkers and CA125 was higher than CA125 alone.[8]

Also, measurement of expression of certain genes helps in assessing the risk of ovarian carcinoma and plays important role in targeted therapy. Kurian et al. concluded that there are eleven genes identified to be responsible in ovarian carcinoma risk, namely ATM, BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, NBN, STK11, RAD51C, and RAD51D[9]. According to study by Norquist et al, the results were similar, but PALD2, BARD1 and PMS2 were identified instead of ATM, NBN and STK11[10.] Risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers begins after age 40 and after age 50 respectively[11] and olaparib, which is an oral poly (ADP-ribose) polymerase inhibitor, is an FDA and EMA approved therapy for BRCA1 and BRCA2 associated ovarian cancer[12].

New therapies have been discovered for ovarian carcinoma, including tyrosine kinase inhibitors, PARP inhibitors, ONX 0801, genetic therapies, and mirvetuximab soravtansine. Besides bevacizumab, an anti-angiogenic agent used in advanced ovarian carcinoma, tyrosine kinase inhibitors (TKI) also inhibit angiogenesis by blocking adenosine triphosphate binding to the VEGFR, thereby inhibiting phosphorylation of the receptor blocking downstream signal transduction. Thus, endothelial cell proliferation cannot take place. TKIs may block compensatory mechanisms which lead to resistance observed with VEGF inhibitors by targeting multiple simultaneous pathways[13]. Cediranib, nintedanib and pazopanib are oral multi-targeted TKIs which have shown encouraging results in Phase III trials[14 – 16]. A significant overall survival benefit has been demonstrated with the addition of concurrent and maintenance cediranib to platinum-based chemotherapy in patients with recurrent platinum-sensitive ovarian cancer[14], while addition of nintedanib to first-line carboplatin and paclitaxel in the AGO-OVAR 12 study led to significant improvement in progression-free survival, with greater benefit seen in a pre-specified low risk sub-group[15]. To date, there has been one Phase III trial of pazopanib in ovarian cancer, demonstrating a progression-free survival benefit in women treated with maintenance pazopanib following primary surgery and systemic therapy[16]. However, hypertension, diarrhoea, hypothyroidism, proteinuria and fatigue are side effects commonly observed in cediranib-maintenance arm; with 22% of patients experiencing grade 3 or more diarrhoea in the nintedanib arm. The most common toxicities reported with pazopanib were hypertension, neutropenia, liver-related toxicity and diarrhoea[13].

Olaparib (a PARP inhibitor) inhibits base excision repair via blockade of enzymatic function, which lead to the induction of double-stranded breaks after stalling and collapse of the DNA replication forks. Tumours in which there is an apparent defect in homologous DNA repair (and thus defect in repair of double-stranded breaks) seem to be susceptible to PARP inhibitor therapy. In a study of 298 patients including 193 patients with platinum-resistant ovarian cancer, the tumour response rate was 26.2%. Responses to olaparib were seen in 30% of patients with ovarian cancer with platinum-resistant disease. Stable disease that persisted 8 weeks was observed in 40.4% of the patients, with overall duration of response of 225 days. However, serious adverse events (fatigue, nausea, vomiting, anaemia, diarrhoea, abdominal pain, headache, dyspepsia, decreased appetite) were seen in 30.1% of ovarian cancer groups, with 10.4% experienced serious effects considered causally related to olaparib[12].

ONX-0801 is a new class of drug discovered that mimics folic acid to enter cancer cells, which then blocks thymidylate synthase, leading to irreparable DNA damage and cancer cell death. It was seen to significantly shrink tumours in seven of the 15 ovarian cancer patients in a Phase I clinical trial. For patients whose tumours had the particular molecular target for the drug, the results were even better – with seven of 10 women responding. Ovarian cancer cells have an abnormally large number of receptors for folic acid, called alpha folate receptors which are particularly targeted by the treatment, while healthy cells are left alone. This means that it can avoid the side-effects often seen with traditional chemotherapy[17].

For patients with medium to high folate receptor alpha-positive platinum-resistant ovarian cancer, an antibody-drug conjugate known as mirvetuximab soravtansine, is a potential treatment currently in phase III trial. It is an antibody – drug conjugate that targets FR-alpha, a cell-surface glycoprotein found on approximately 80 per cent of epithelial ovarian cancer tumours. In a phase 1 expansion study, mirvetuximab soravtansine demonstrated a confirmed objective response rate (ORR) of 26 per cent among 46 patients with FR-alpha – positive platinum-resistant ovarian cancer, including one complete and 11 partial responses. While, the median progression-free survival (PFS) was 4.8 months and the median duration of response was 19.1 weeks. The commonly observed treatment-related toxicities include diarrhoea, blurred vision, nausea and fatigue, with neuropathy observed in less than 10 per cent of patients[18].

Studies have identified many oncogenic miRNAs (oncomiRs) and tumour suppressor miRNAs (tumour suppressor miRs) expression in ovarian cancer. Treatment options for ovarian cancer include supplementation of miRNAs that are downregulated in cancer tissue for recovery of function and inhibition of the function of upregulated miRNAs by administration of complementary nucleic acids. Garzon et al. showed that antagomir, an oligonucleotide complementary to the miRNA administered as an antisense oligonucleotide or LNA can suppress the effects of upregulated oncomiRs[19]. Lu et al. developed an anti-miRNA antisense oligodeoxyribonucleotide (MTG-AMO) for suppression of many miRNAs, including miR-21, and was effective in cancer with concurrent multiple mRNA abnormalities[20]. Dai et al. established a therapy by targeted delivery of miR-29a to cancer tissues for the purpose of reexpressing PTEN on the basis of expression of downstream molecules and apoptosis of ovarian cancer cells[21].

CONCLUSION

The current meta-analysis showed that NACT helped the gynaecologic oncologist achieve an increased rate of optimal cytoreduction, and NACT should be considered in patients who are likely to develop postoperative

morbidity and mortality. However, new treatments have been discovered for ovarian carcinoma including tyrosine kinase inhibitors, PARP inhibitors, ONX-0801, genetic therapies, and mirvetuximab soravtansine. Also, genomic tests not only help in assessment of susceptibility to ovarian carcinoma, but also potentially aid in targeted therapy. Thus, further studies are needed to determine the effectiveness of new therapies in the management of advanced-stage ovarian cancer.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this case.

CONSENTS

Written informed consent was obtained from the patient to publish the case. A copy of written consent is available for review by the Chief Editor.

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