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Title of the Thesis: Study on MAD and BUB1 genes of spindle assembly checkpoint with response to primary adjuvant chemotherapy in advanced epithelial ovarian cancer

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ABSTRACT

Ovarian cancer is a multifactorial disease with poor chances of successful treatment and survival time. Carboplatin and Paclitaxel is the preferred treatment for ovarian cancer patients with advanced stage (III & IV) tumors. The spindle assembly checkpoint (SAC) was activated by both Carboplatin and Paclitaxel that triggers mitotic arrest and subsequent apoptosis in ovarian cancer cells *in vitro*. So, the present study analysed the expression of MAD1, MAD2, BUB1 and BUB3 and a few SNPs in were selected to correlate with clinical response, safety of chemotherapy and 2-year survival outcomes. The methods included clinical assessments, histology, immunohistochemistry (IHC) and PCR-RFLP, sanger sequencing and qRT-PCR. The results showed that majority of the patients were in the age range of 41-60 years, presented with abdominal complaints, nausea, vomiting, fever, and pelvic symptoms. Serous was the most observed histological subtype (81%). Most of the tumors were large at the time of diagnosis and platinum sensitive (ORR= 77·27%). 41, 44 and 25 patients were categorized as responders, partial responders, and non-responders. The standard regimen was well tolerated but Grade 3/4 toxicities in anemia, anxiety/depression, diarrhoea, and constipation were observed with deteriorated quality of life. They experienced significant neuropathy and movement-associated pain. The overall survival for responders, partial responders and non-responders were significantly different ($p<0·05$) with CA125, age, parity, menopausal age and occupation being significant baseline risk factors (HR>1). The findings of this study highlight the downregulation of MAD1 and BUB1 with upregulation of MAD2 and BUB3 as the signature feature in advanced ovarian cancer. MAD2 expression was significantly associated with poor OS. MAD2, BUB1B SNPs had significant relevance to chemo-induced toxicity. In addition, Association of the miRs analysed showed significant impact on survival outcome either independently or in correlation with a SAC component.

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