Name of the Research Scholar: Ankita Leekha
Name of the Supervisor: Prof. M. Moshahid Alam Rizvi
Department: Department of Biosciences, Faculty of Natural Sciences, Jamia Millia Islamia, New Delhi-110025
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Abstract

Ovarian cancer remains a deadly malignancy because most patients develop recurrent disease that is resistant to chemotherapy, including platinum. Currently, resistance can only be determined retrospectively after patients have experienced the burden and toxicity of ineffective therapy. The majority of ovarian cancer patients respond to initial therapy with tumor cyto-reductive surgery and platinum-based chemotherapy. However, approximately 70% of advanced stage patients will develop recurrent cancer and eventually succumb to recurrent disease typically characterized by multiple drug resistance. Nevertheless, platinum-based chemotherapy remains the mainstay for treatment of recurrent disease. Due to the poor survival of women with platinum-resistant ovarian cancer, understanding the mechanisms contributing to platinum resistance as well as improved therapeutic approaches are urgently needed.

Cisplatin is among the most widely used broadly active cytotoxic anticancer drug; however, its clinical efficacy is often limited by primary or the development of secondary resistance. Several mechanisms have been implicated in cisplatin resistance, including reduced drug uptake, increased cellular thiol/folate levels and increased DNA repair. The use of cisplatin in cancer chemotherapy is limited by acquired or intrinsic resistance of cells to the drug. Platinum-based chemotherapeutics elicit their cytotoxic effects by forming intra-strand cross-links of DNA and platinum that induces cell apoptosis. Most of the platinum-based combination therapies in our analyses are fundamentally expected to have the additional benefit of targeting one of the major

mechanisms of platinum resistance (i.e., enhanced repair mechanism of damaged DNA). Now-a-days, developing mechanisms to either increase the uptake of cytotoxic agents into tumor cells or improve retention of cytotoxic agents within tumor cells may be an attractive approach to overcome platinum resistance.

The focus of this thesis was to identify a combination therapy to address cisplatin resistance as it was detrimental in the successful management of ovarian cancer. Present work was focussed on restoring the cisplatin-sensitivity in cisplatin-resistant cell line. Since, the biochemical properties of cancer cells and normal cells are different, we targeted the redox-modulating strategies to enable therapeutic selectivity by using natural agents in combination with Cisplatin (CP) and Gemcitabine (GB) so as to abrogate the adaptation mechanisms. This was as an attractive new approach to improve the therapeutic outcomes. Vitamin C (VC) is a versatile natural anti-oxidant and it possess the potential of reversing the chemoresistant phenotypes and preferentially targeting the cancer cells at only pharmacological doses. Our aim was to target DNA repair mechanisms as an attractive therapeutic approach in platinum-resistant ovarian cancer.

Therefore, combinatorial therapy induced cell death was enhanced generation of ROS that caused ER stress, alterations in $\Delta\psi m$, release of Cyt.c from mitochondria and release of pro-apoptotic proteins that lead to apoptosis in PA-1 and CaOV-3 cells. Our study is the first to demonstrate that the natural plant product "Vitamin C" when combined with Cisplatin and Gemcitabine therapeutic regimen boosts the cell death of platinum-resistant ovarian cancer cells by the Reactive Oxygen Species-mediated mitochondrial apoptosis pathway in PA-1 and CaOV-3 cells but not in the normal cells (HEK) that makes Vitamin C a better choice as a combination agent to be used with conventional cytotoxic drugs. These compelling results expanded our understanding that might be helpful for the development of Vitamin C into a chemotherapeutic drug for treatment of cisplatin-resistant ovarian cancer.