

## **Abstract**

The incidence of ovarian carcinoma in the Czech Republic is one of the highest in the EU. The five year survival rate of all stages is approximately 40%. The mortality still remains high globally, despite the efforts of diagnostic procedures and modern treatment. After ending the course of chemotherapy, a completely successful clinical response can be achieved in the early stages (stage I. a II.) in almost 100% of patients. However in 20-40 % it is unfortunately impossible to completely eliminate all tumour cells resistant to chemotherapy and almost a third of women have relapses. Today in the late stages (III. a IV.) more than 70 % of cases result in complete clinical remission; however within 2 years more than 50 % of women from this group suffer from relapses. The relaps of disease results from the activation of a chemoresistant clone of malignant cells. Those cell populations that aren't detectable using investigation methods are marked as minimal residual disease. The issue has been divided into three areas. In the first we monitored the amount of regulatory T-cells in peripheral blood of patients with ovarian cancer. In the second we monitored the dynamics of the immune infiltrate, depending on the stage of the disease. In the third, we tested various types of cytostatics in their ability to induce tumor-specific immune response. In some series of malignant tumours multiple peripheral CD4+CD25+ T lymphocytes (Treg) were found. Treg play a suppressive role in the control of antitumour immunity. In some tumours the percentage of Treg cells in peripheral blood were found to correlate with the patients' prognosis. One of the experimental procedure in consolidatory treatment is usage of peroral low etoposid or cyclophosphamide dosages. Low (metronomic) dosages don't have a direct cytotoxic effect on chemoresistant tumour cells but from many experimental animal studies cyclofosfamide was found to have a positive effect on this low doses treatment in stopping growing tumours and their regression - eventually removing disease relapse. In this study we confirmed that the patients with stages I/II of the disease had an excellent prognosis and very good outcome in stage IIIC patients with no residual tumor after surgery. There was no difference in the PFS of patients with residual tumor after surgery, irrespective of the consolidation therapy received. Patients with the early relapse had significantly faster kinetics of the rise of Tregs in the peripheral blood, which translated into the higher slope of Tregs trend line. The slope of the Tregs trend line was a significant predictor of an early relapse. The slope of Tregs trend line does not have any predictive value for late relapses. In the second part of the research we found out that Tregs in the tumor varies significantly in different stages of the disease. In advanced stages, chemotaxis of Tregs occurs from peripheral blood in tumor tissue and these Tregs contribute significantly to increase the

immunosuppressive microenvironment within the tumor. In the third part of the research we found out that tumor cells killed by anthracycline induced immunogenic death significantly more than the tumor cells killed by UVA radiation or killed by the other types cytostatics.

Keywords: ovarian cancer, Regulatory T cells, Metronomic chemotherapy