Effects of Antiangiogenic Agent Bevacizumab on Over Cancer Cell Culture (Ovcar-3) Alone and Combined with Classic Chemotherapeutics

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Abstract

Background: Cancer is an important problem that has serious effects on the quality of life. Despite advances in diagnosis, it still affects millions of people. Ovarian cancer is the most common cause of gynecological cancer deaths; it has a very important place in gynecological oncology. Combination therapy is a treatment method that

SPSS program was used in the statistical evaluation of the results. One-way ANOVA and Tukey test as a post-hoc were used. The significance limit was determined as $p<0.05$.

Results

At the end of 72 hours, a significant decrease was observed in all doses of carboplatin according to control. This reduction is 20% at 50

a decrease on IRS, COX-2 and VEGF gene levels. The data obtained in the combined applications showed that they are not as effective on gene activations as single applications. (Bevacizumab was not included in the analysis as it was found to have no effect on ovcar-3 cells.

Discussion

Drug candidates that fail in the clinical development process cause serious financial investment, resource and time losses. For this reason, studies conducted in cell culture can increase the chance of success as well as prevent waste of resources. In drug development studies, pharmacological activities of drug candidates are almost always tested in cell culture [14,15].

Apoptosis is involved in many biological processes and is one of the most frequently used areas of research on cell biology. Apoptosis can be accurately detected with the MTT staining method. DAPI staining method is frequently used to determine the apoptotic effect morphologically. Caspase chain has an important role in the regulation of apoptosis. The released cytochrome C activates caspase-3 [16].

Paclitaxel acts by preventing cell division and polymerization through microtubules, thus apoptosis occurs. Paclitaxel also has angiogenic inhibitory effects by suppressing VEGF expression. Carboplatin is an anticancer drug it triggers apoptosis. Apoptosis acts through the activation of a family of cysteine proteases called caspases. Apoptosis occurs with the activation of caspases such as caspases 3 and 7 [17-20].

In our study, carboplatin reduced the viability of ovcar-3 cells at all doses on the second and third days. In similar studies in the literature, the results are similar to those obtained in our study. In some randomized clinical studies, Paclitaxel combination with cisplatin or carboplatin was compared in patients with advanced ovarian cancer. It has been observed that the treatment regimen in which carboplatin is used in combination is more tolerable. According to the results of another study, the viability of cells treated with Docetaxel +carboplatin, docetaxel+PNP-GDEPT and carboplatin+PNP-GDEPT and the combination of three agents was examined. The greater reduction occurred in the case of the combination of all three. Increased sensitivity of resistant ovcar-3 cells to docetaxel and carboplatin has been observed when included in PNP-GDEPT combination regimens. It has been found that this occurs through increased apoptosis as a result of down-regulation of genes responsible for the drug resistance mechanism [21,22].

In our study, paclitaxel reduced the viability of ovcar-3 cells at all doses on the first, second and third days. The results obtained in similar studies are similar to the results of our study. In a study, MCTS (multicellular tumor spheroids) were used because conventional cell culture methods may not fully reflect the clinical features of the disease. Paclitaxel showed a much weaker effect in MCTS compared to 2D cultures. Following this process, licofelone, which is predicted to have a synergistic effect with paclitaxel, was combined with paclitaxel and applied to the cells. The combination has been found to have a significant synergistic effect [23].

In our study, it was observed that the combination of paclitaxel +carboplatin showed the most significant effect in the first 24 hours at low doses (2.5 nM and 50 µM, respectively).

In another study, paclitaxel was combined with Silibinin and applied to ovarian cancer cells. MTT analysis was performed. The results showed that cell proliferation was sharply inhibited by paclitaxel. Combined therapy, on the other hand, had a greater effect than drugs alone. The doses used in the combination are IC50 dose determined for paclitaxel and lower than IC50 for Silibinin. This means that the drugs are used in combination at low doses. The P53 and P21 gene expression at different concentrations of the combination of Silibinin and paclitaxel showed a significant difference compared to control cells [24].

In our study, it was determined that paclitaxel and carboplatin increase the activity of caspase-3 alone or in combination. It has been observed that this increase is more pronounced at the end of 12 hours than at the end of 24 hours. After twelve hours, the most significant increase was noted in paclitaxel at a dose of 5 nM. At the end of 24 hours, it was observed in 50 µM dose of carboplatin. This increase in paclitaxel and carboplatin is more pronounced than combined applications.

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In a study in the literature, the results of MTT and caspase-3 analysis were examined by combining carboplatin and paclitaxel with another drug. The results demonstrated the superiority of combination therapy over individual treatments at each dose in cell viability. The interesting finding found here was that the greatest reduction in cell viability occurred at lower doses compared to higher doses. Similar determinations were made in our research, an example of this is that in the caspase analysis, carboplatin at a dose of 100 µM and paclitaxel at a dose of 5 nM give more effective results than combinations. In the same study, expression of annexin V and caspase 3 activity were investigated. Significant increases in annexin V expression and caspase-3 activity were detected after carboplatin and paclitaxel treatment. When the agent which is the third member of the combined

ovarian cancer cells. In another study, it was reported that high hypoxia-inducible factor-1α (HIF1α) upregulates bevacizumab resistance genes, limiting the efficacy of bevacizumab targeting the VEGF pathway [31-33].

It is known that angiogenesis induced by VEGF plays a key role in cancer development. IRS-1 supports tumor growth, but the mechanism is not fully understood. Ki-67 expression is associated with common histopathological parameters. COX-2, catalyzes the first step in the formation of prostaglandins [34-37].

The results obtained in our study showed that paclitaxel and carboplatin, when used alone, affect the factors mentioned above to decrease. These results are in line with the findings obtained in previous studies on the subject. In our study, different from other studies, various combinations of paclitaxel and carboplatin did not show the expected effect on the factors.

Conclusion

In our study, bevacizumab showed no anticancer effects in MTT, DAPI Staining, caspase-3 and Real-Time PCR analyses in ovcar-3 cancer cell lines alone and combined. This is different from some

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