INTRODUCTION

Malignant Trophoblastic Disease is a type of malignant tumor cells that have a nature relatively sensitive to chemotherapy. Problems are often encountered in handling chemotherapy gestational trophoblastic neoplasia (GTN) which are a process that requires several cycles of chemotherapy and a relatively long course also requires a relatively highly cost. Therefore a method or an alternative therapy that is expected to shorten the time of chemotherapy or reduce the number of cycles needed to achieve optimal initial response is needed, so it can provide benefits to patients both in terms of time or cost.

In the case of low risk GTN by administering a single chemotherapy methotrexate (MTX) to achieve complete remission, until the beta hCG is below the value of 5 mIU/ml, the required cycles are ranged from seven to twelve cycles of chemotherapy or within about 4 to 6 months, with a success rate of therapy in achieving complete response approximately 84%.1

The risk of malignant degeneration in patients hydatidiform mole is approximately 15 - 28%. Clinically malignant degeneration is referred as GTN or persistent hydatidiform mole. The morbidity such as bleeding, infection, and the failure of reproductive function with a mortality rate reaching 9%. GTN occurs alleged in the genes that regulate cell proliferation, genes that regulate apoptosis, and patient’s immune factors.1,2

Cell proliferation is controlled by genes acts on the cell cycle. Proliferation will run sustainable if the genes that induce cell cycle proliferation have sustained...
stimulation. Degeneration of malignancy in hydatidiform mole is called persistent mole or GTN.

The mechanism of apoptosis is a protective mechanism in human. Apoptosis is a programmed cell death. The mechanism of apoptosis occurs when gene abnormalities repair has failed. When repair and apoptosis fail, there will be a proliferation of mutant cells. This will lead to the process of malignation. Vitamin A has a role in regulation of cell proliferation, cell differentiation and apoptotic activity. Low levels of vitamin A causes a disruption of control mechanisms on proliferation and cell differentiation. The effect of vitamin A on proliferation or cell differentiation remains unclear. Suspected role of vitamin A in controlling proliferation is through p53 causes G1 arrest and pRB causes S phase arrest.

Vitamin A activity is known to inhibit proliferation and stimulate apoptosis of several cancer cells has been demonstrated in laboratory studies, and on clinical research. Vitamin A has been used as preventive therapy for post-hydatidiform mole malignancies, supportive and adjuvant therapy for some cancer types.

Clinical studies on the influence of vitamin A in combination with chemotherapy for the treatment of GTN has yet been done. This study aims to determine the effect of the combination of MTX and vitamin A to decrease serum levels of beta hCG in the treatment of low risk GTN compared to administration of MTX alone.

**METHOD**

This study used a double blind randomized clinical trial design by comparing the decrease of serum levels of beta hCG in patients with low risk gestational tropho-blastic tumors who were given chemotherapy of MTX 50 mg only compared to patients who received combination chemotherapy of MTX 50 mg and vitamin A dose of 100,000 IU/day for three cycles.

Research has conducted on 20 patients who met the inclusion criteria of GTN, which was divided into 10 patients each group, the control group who received MTX chemotherapy and the other who received MTX chemotherapy and vitamin A.

Each patient of low risk GTN that had been planned for chemotherapy with MTX 50 mg who met inclusion and exclusion criteria, first got a detailed explanation about the study procedures and voluntarily signed the informed consent form.

Allocation the subjects into groups was conducted by block randomization.

In this study, the subjects were performed the examination of beta hCG concentrations by taking blood samples for examination materials. Pre therapy of beta hCG level were first determined and serial beta hCG examination were conducted every two weeks at the end of each cycle of chemotherapy. Vitamin A was given at 100,000 IU dose per day during the study (three cycles of MTX chemotherapy, approximately six to seven weeks).

MTX 50 mg was given according to the standard procedures in Oncology Department of Dr. Hasan Sadrkik Hospital. In one cycle of chemotherapy, MTX 50 mg was given intramuscularly for eight days. MTX was given on day 1, 3, 5, and 7, while folic acid was given on 2, 4, 6, and 8. The results of the study was recorded after three cycles of chemotherapy. MTX chemotherapy was given by doctor on duty in the oncology ward. Blood sample was to the laboratory. Data was analysed using SPSS 17.0 for Windows.

**RESULTS AND DISCUSSION**

Table 1. Characteristics of study subjects.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control Group (N = 10)</th>
<th>Treatment Group (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean</td>
<td>28.10 (SD 4.408)</td>
<td>27.30 (SD 4.877)</td>
</tr>
<tr>
<td>• Range</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 0</td>
<td>2 (20%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>• 1</td>
<td>4 (40%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>• 2</td>
<td>3 (30%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>• 3</td>
<td>1 (10%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Pre therapy beta hCG level (mIU/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mean</td>
<td>52215.5 (SD 23743.64)</td>
<td>59349.5 (SD 29072.82)</td>
</tr>
<tr>
<td>• Median</td>
<td>53349.50</td>
<td>61319</td>
</tr>
<tr>
<td>• Range</td>
<td>(18993 - 89365)</td>
<td>(18806 - 98291)</td>
</tr>
</tbody>
</table>

Mean SD p Difference IK 95%

MTX 473.12 249.69 0.000 423.67 243.96 - 603.38
MTX + Vitamin A 49.44 42.94

Table 2. Serum beta hCG levels after three cycles of chemotherapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>Complete Remission</th>
<th>MTX Resistance</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>–</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Treatment</td>
<td>2</td>
<td>–</td>
<td>20</td>
</tr>
</tbody>
</table>

From the calculation results obtained the average levels of serum beta hCG after three cycles in the treatment groups were lower than the control, 49.44 mIU/ml and 473.12 mIU/ml, respectively. The statistical analysis using 95% degree of confidence shown a significant difference (p < 0.001).
In the treatment group there were two patients (20%) who achieved complete remission and in the control group, there was one patient (10%) who had resistance to MTX, shown in Table 3.

The independent variable was vitamin A and confounding variables were age, parity and levels of beta hCG pre therapy. Only vitamin A influenced and had a significant correlation of decreased levels of beta hCG. Based on that, it can be concluded that vitamin A help accelerate the decline in serum levels of beta hCG in patients with low risk GTN who received MTX.

Clinical study regarding the administration of vitamin A combined with MTX chemotherapy for the treatment of GTN has yet been done. Yamada et al, and Chiu et al, had been conducting research in vitro associated with providing a combination of MTX and vitamin A. The research was conducted in the laboratory by examining the effect of vitamin A in choriocarcinoma cell division and apoptosis. Vitamin A in this study may provide a synergistic effect or potentiation of MTX on choriocarcinoma cell growth resulting in greater resistance to cell division rather than the development of choriocarcinoma cells which only received MTX without vitamin A.

Action mechanism of vitamin A in suppressing the growth of cancer cells to GTN is through increased activity of p53 that caused the stop on the G1 phase.11,12 While other mechanisms in suppressing the growth of cancer cells to GTN is through CRABP-II complex with RAR α, by activating p21 and p27, which is one of the tumor suppressor gene. Activation of p21 and p27 will lead to stop at G1 phase and continuous S phase.11,12

Vitamin A also promotes apoptosis in cells through an activation and elevation of p53, subsequently lead to inhibition of the expression c-myc and Bcl-2. This mechanism would encourage apoptosis.11

In this study, chemotherapy of MTX would theoretically lead to a deficiency of thymidylate synthase and inhibit purin synthesis. De novo synthesis process will lead MTX to resist in cell division induced cytotoxic effects on cells, especially at S phase in the cell cycle.13 Some of the reactions occurred after administration of MTX will further lead to cessation of synthesis DNA, RNA, cell replication and protein synthesis and this will further suppress the growth of cancer cells in GTN.14 Giving vitamin A and MTX will potentiate the action in accelerating the response to therapy in suppression of cancer cell growth and this was shown by the accelerated decline in serum levels of beta hCG.

RESULT

A decline in serum levels of beta hCG was significant after three cycles of chemotherapy in the treatment group than the control group (p < 0.001). The mean levels of serum beta hCG after three cycles of chemotherapy in the control and treatment groups respectively were 473.12 mIU/ml and 49.44 mIU/ml. Complete remission after three cycles of chemotherapy achieved in two patients (20%) of the treatment group resistance to MTX occurred in one patients (10%) in the control group.

CONCLUSION

Giving MTX chemotherapy in combination with vitamin A in patients with low risk GTN may potentiate the decline of beta hCG serum level compared to MTX chemotherapy alone.

REFERENCES

6. Andrijono. Prevention of malignancy following hydatidiform mole with high-dose vitamin A. [Dissertation]. Faculty of Medicine Indonesia University; 2007