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TREATMENT OF GESTATIONAL TROPHOBLASTIC DISEASE - REVIEW OF LITERATURE

Biljana Lazović and Vera Milenković

Gestational trophoblastic disease (GTD) is characterized by abnormal proliferation of pregnancy-associated trophoblastic tissue with malignant potential. GTD covers a spectrum of tumors and tumor-like conditions and may occur in a benign form as hydatiform mole or as malignancy in the form of invasive mole or choriocarcinoma. GTD has become a curable malignant disease since the introduction of chemotherapy. Optimal therapy in this group of diseases rests in the correct diagnosis, assessing their risk for malignant behavior using prognostic scoring systems and administering appropriate treatment. Their rarity makes it imperative that these patients are treated in special centres by experts. Benign moles are treated surgically with evacuation of the uterus or hysterectomy. In malignant gestational trophoblastic disease, chemotherapy is the treatment of choice; single agent for non-metastatic and low-risk metastatic disease and a combination chemotherapy for high-risk metastatic disease. Judicious use of surgery and radiotherapy in these cases will improve the survival rate. With appropriate treatment, the cure rates approach 100% in the low-risk group, and 80% to 85% in the high risk group. By applying the aquired knowledge and experiences, we could not accept to lose any patient because of gestational trophoblastic diseases. Acta Medica Medianae 2010; 49(1):64-69.

Key words: *chemiotherapy, gestational trophoblastic disease, surgical treatment, radiation therapy*

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Introduction

Gestational trophoblastic disease may be benign or malignant. Histologically, they are classified as hydatidiform mole, invasive mole, choriocarcinoma and trophoblastic tumor of placental site. Generally, they are known as gestational trophoblastic neoplasia, except trophoblastic tumor of placental site, which is described as a separate entity, because the clinical features, treatment and prognosis are different. Hydatidiform mole is the most common manifestation of this disease. While invasive mole and choriocarcinoma are only malignant forms, hydatidiform mole may be benign and malign (1).

Over the years, there have been different systems of trophoblastic disease classification. At the XVI FIGO World Congress of Gynecology and Obstretrics 2000 in Washington, the classification of GTN was accepted as a combined staging / scoring system, known as the FIGO / WHO system (International Federation of Gynecology and Obstetrics / World Health Organization). 'Staging' is based on anatomical criteria, which classifies the disease into four stages (2):

- Stage I - the disease is limited to the uterine body
- Stage II - includes other genital organs
- Stage III - metastasis to the lungs
- Stage IV - other metastases

Each stage is further divided on the basis of prognostic scoring index tosubstage A or B. If the risk factors are not known, there is no division into substages. If prognostic score is 7 or less, the substage is A, while substadium B corresponds to prognostic score almost 8 or higher.

Prognostic scoring index is based on the scoring system from 0-4, depending on the presence of prognostic factors:

Table 1. Combined FIGO staging and WHO scoring system

	0	1	2	4
	≤ 39	≥ 39		
Age (years)	Hidatiformna mola	Abortus	Terminska trudnoća	
Previous pregnancy	4	4 - 6	7 - 12	> 12
Interval from index pregnancy (months)	10^3	10^3-10^4	10^4-10^5	>10^5
Pre-treatment Beta hCG (iu/ml)		3– 4cm	5cm	
Larger tumor size(cm), including uterus		Spleen, kidney	Gastro-intestinal	Brain, liver
Broj identifikovanih metastaza		1 - 4	4 - 8	> 8
Prethodno neuspela hemioterapija			Single	Two or more drugs

The disease is considered as low risk situation with a score 6 or less, and high risk with a score 7 or more.

However, for more effective treatment, from the aspect of gynecologists-ractitioner, clinical classification according to prognostic factors is of the greatest importance. This system is the basis which most of the major centers for trophoblastic disease in America use to determine the treatment and assess the results achieved. Patients with GTN were divided into three groups:

1) with non- metastatic disease
2) low-risk metastatic disease
3) high- risk metastatic disease

High risk refers to the patient that is not likely to be cured with a single-agent chemotherapy, and which bears the highest risk of treatment failure.

Before the determination of prognostic factors and establishing treatment criteria, it is necessary to identify a group of patients with life-threatening complications. Frequently, it is difficult intraperitoneal vaginal bleeding or respiratory disorders which lead to pulmonary metastases. This complication needs to be resolved immediately, before determining chemiotherapeutic regime (3,4).

After exclusion of life-threatening complications, it is necessary to create a strategy that offers the best prospects for eradication of tumors in the shortest period of time, with minimum toxicity. The basis of this approach is classifying patients into appropriate risk categories. Duration of therapy will be different for each patient; in some of them, resistance to drugs develops, which further requires a change of chemotherapeutic drug.

Measuring of serum hCG twice a week provides the basis for making decision for each case separately, as well as hCG decrease rate, and when its value becomes normal, there should be calculatated for how long it is necessary to administer chemotherapy in order to decrease the number of tumor cells to zero. Based on the assumptions, when the value of hCG falls on the border value of the most sensitive tests, that means that there are still 104 to 105 of viable tumor cells. Normally, hCG should decrease by half a logarithm with each cycle of chemotherapy. Every decrease less than the above points to a certain degree of resistance to drug. Very slow decline in the value of hCG, or continuous increase is the indication for a change of therapy (5, 6).

Treatment of non-metastatic trophoblastic disease

Non-metastatic disease is most common trophoblastic disease. According to the definition, it is limited to the uterus, and according to FIGO classification, it refers the patients with early stage of disease.

About 75% of patients have invasive mole, and 25% have choriocarcinoma.

Hysterectomy can be advised as initial treatment if it is not necessary to preserve fertility, or if placental site trophoblastic tumor has been diagnosed. Sing-agent adjuvant chemotherapy is indicated at the time of surgery to eradicate any occult metastases, reduce the probability of dissemination of vital cells, and maintain cytotoxic levels of chemotherapeutic drugs in tissues and plasma, if dissemination of viable cells during the hysterectomy occurs. Hysterectomy is necessary in less than 5% of cases, which results in preservation of reproductive function in about 95% of patients.

Single-agent chemotherapy is the treatment of choice for the patient wishing to preserve the reproductive capacity. There are several chemo-therapeutical protocols in use, and all are excellent and can reach comparative remission rates (6).

Methotrexate 0.4 mg / kg (maximum 30 mg) i.v. or i.m. per day during 5 days in one cycle of therapy is the treatment of choice. Also, the alternative mode is applied, in which slightly higher dose of methotrexate is given, 1,0-1,5 mg / kg im every other day four times, with folic acid 0,1-0,15 mg / kg im given 24 hours after each dose of methotrexate.

The advantage of this protocol is the ease of application and reduced toxicity. Methotrexate may be given in a single weekly dose of 30mg / m² and the results achieved by this method are somewhat poorer. Methotrexate is metabolized in the liver, and therefore, its application during the liver disease or imbalanced renal functions are contraindicated. During the application of methotrexate, alopecia does not appear, ulceration in the mouth occurs rarely and usually in patients who take less than 2-3 l of fluids per day. In some patients pleural pain appears, vaginal and rarely perineal ulceration. Allergic manifestations are very rare. Methotrexate causes photosensitivity, so that patients who receive it are advisable to avoid sunbathing.

Aktinomicin-D 10-12 mikog / g i.v. a day for five days in a cycle every other week is alternatively applied and stands for the appropriate regimen for patient with liver or renal diseases, in the case of which the use of methotrexate is contraindicated. Also, aktinomicin-D can be given as a single dose of 1.25 mikog / m² iv every two weeks, after which satisfactory results are obtained. System side effects of this drug are similar to those in cases of methotrexate. Aktinomicin-D should be given slowly, over 5-10 minutes through the appropriate veins, because extravasation leads to necrosis and demarcation of tissue.

Often, a combination of individual chemo-therapeutical drug is applied (sequential single-agent chemotherapy), which involves alternate administration of different drugs, thus avoiding the cumulative toxicity of a drug and slowing down the development of resistance (7,8).

Treatment continues until three consecutive normal hCG-titres are achieved, and two more cycles can be given after normal levels of hCG are reached. Irrespective of the drug applied, the next cycle of therapy should be applied depending on the laboratory analysis, which should be done every 7-14 days. Duration of the therapy should be determined by the level of hCG, blood count, the

number of leukocytes, the number of platelets and SGOT. New cycle of chemotherapy should not be started if the number of leukocytes is less than 3000/ml, the number of granulocytes less than 1500/ml, the number of platelets below 1 000 000/ml or SGOT values higher than 50 units.

Chemotherapeutical drug should be changed if the level of hCG is maintained or toxicity does not allow adequate doses. If there is a significantly increased level of hCG or if metastases appear, then combined (multiagens) therapy is the therapy of choice.

Treatment of low-risk metastatic trophoblastic disease

Therapy with a single agent (single-agent treatment) with methotrexate or aktinomicinom-D is conducted in the same manner as described for non-metastatic disease. The advantage of a single-agent therapy is its lower toxicity and reduced possibility of irreversible consequences, compared to treatment with multiple agents. If a patient develops resistance to single-agent therapy, there will be introduced a combined chemotherapy for a high-risk disease. Hysterectomy may be necessary to eradicate persistent, to chemiotherapy resistant uterine disease, or can be done as an adjuvant treatment simultaneously with the introduction of chemotherapy to reduce the duration of treatment. It has been noticed that patients with good prognosis of metastatic disease, in whom hysterectomy was performed, with combined treatment with chemotherapy, needed less time and fewer cycles of chemotherapy to come into the state of remission, compared to female patients treated with additional secondary chemiotherapy or those treated with chemotherapy only (9-11).

If a proper treatment is applied, the rate of healing in this group of patients reaches 100%. In 40-50% of these patients, resistance to the first chemiotherapeutical agent occurs and they need alternative treatment. It is therefore important to carefully monitor the patient receiving chemotherapy, to detect resistance to drug, and switch to another agent as soon as the need arises. Approximately, 10-20% of patients treated for metastatic disease of low risk by sequential single-agent chemotherapy to achieve remission require combined chemotherapy, with or without surgical procedures (9).

Treatment of high-risk metastatic trophoblastic disease

Treatment of metastatic trophoblastic disease with high risk is conducted with multiagent therapy. There are several protocols for its use (12-14):

1. MAC. Multiagent regime that consists of 15 mg iv or im, metotrexate, 0.5 mg aktinomicina-D and ciklofosfamida 3mg/kg iv hlorambucil or 10 mg (MAC). Folic acid is in use as a protective factor with methotrexate. Time interval between cycles is 9-14 days. Using the initial MAC protocol for treating high-risk patients, healing rates were recorded from 63-80%.

2. CHAMOCA. Mid-seventies, Bagshaw introduced a protocol that consists of seven drugs: hydroxyurea, aktinomicina-D, methotrexate with folic acid, cyklofosfamid, vincristine (oncovin) and doxorubicin (adriamycin) (CHAMOCA). Using this protocol, the authors have achieved a healing rate of 82% in patients treated for primary disease. Clinical comparison of MAC protocols and CHAMOCA has shown that the healing rate is higher in patients who were initially treated with MAC (95%) compared to patient treated with CHAMOCA (70%) protocol, and that the toxicity is much less with the first protocol application.

3. EMA-CO. After discovery that etopozyd (VP 16-213) is a very effective way for the treatment of GTN, Bagshaw formulated the EMA-CO protocol, which is composed of: etopozyd, infusion of high doses of metotrexate with folic acid, aktinomycina-D, cyklofosfamida and vincristina. Establishing the existence of brain metastases, dose methotrexate in this mode is increased to 1 g / m² with folic acid (30 mg) every 12 hours over three days from the start of methotrexate infusion. This protocol proved to be extremely effective and relatively non-toxic. With its application, survival is achieved in 83% of patients initially treated with this combination. Nowadays, the EMA-CO protocol is the treatment of choice for high-risk patients. Chemotherapy continues until three consecutive normal hCG titres are obtained, and is usually given after the first normal titre in at least two to three following cycles.

Toxicity during the application of combined chemotherapy was significantly higher compared to single-agent chemotherapy. Leucopenia and thrombocytopenia are sometimes very strong. Vincristin has neurotoxic action and can cause tissue damage if it comes to extravasal application of this drug. Also, nausea and vomiting of moderate severity may occur.

Secondary chemotherapy provides poor results. Cysplatinum and bleomicin are another chemotherapeutical agents with proven activity for trophoblastic tumors. The combination of these agents with etopozyd and vinblastin resulted in healing of some patients in whom the initial combined chemotherapy failed.

4. ICE. New chemotherapeutical protocols containing etopozyd, carboplatynum and ifosfamid with resection of the site resistant to chemotherapy in most cases resulted in healing.

New technologies, such as the application of the factors that stimulate the growth of colonies, reduces disposal of chemotherapeutical treatment and reduction of drug doses, and with autolog bone marrow transplantation play an important role in future treatment of patients in whom the resistance to drugs is apparent. Finding new chemotherapeutical protocol is the goal which today tends to treat trophoblastic disease resistant the conventional chemotherapy.

The importance of applying appropriate initial therapy based on an assessment of the risk of tumor resistance to treatment is clear if we compare the remission rate of 70% in patients with poor prognosis initially treated by combined

chemotherapy, and only 14% in patients who received the combination therapy only after the emergence of resistance to single-agent chemotherapy.

Radiation therapy

In patients with metastatic disease with poor prognosis, during 10-14 days, chemotherapy should be implemented as well as the whole brain radiation therapy, up to a total dose of 3 000 rad / or radiation of the whole liver to the total dose of 2 000 rad.

Surgical treatment

Nowadays, surgery is an important additional treatment to chemotherapy. The role of surgery will be changed with new modern chemotherapeutic protocols, but it still remains the main treatment in patients with persistent trophoblastic disease which poorly responds to chemotherapy.

Surgical technique for the evacuation of molar pregnancy includes curettage and hysterectomy. General indications for surgical treatment for hydatidiform mole are: evacuation of the uterus with intact mole or incomplete abortion, while hysterectomy is performed in patients older than 40 years, in selected cases of invasive mole, perforation of the uterus, in cases where it is not necessary to preserve the reproductive function, in uterine, vaginal, or intraperitoneal heavy bleeding, excision and treatment of isolated perforated uterus caused by invasive mole, and where it is desirable to preserve the reproductive function.

Adjuvant surgical procedures, especially hysterectomy and thoracotomy may be useful for the elimination of disease resistant to chemotherapy, control of bleeding, bowel obstruction, or removal of urinary tract, treatment of infection or treatment of life-threatening complications. Surgery has the primary role in the treatment of placental site trophoblastic tumor.

The value of hCG beta subunit, a reliable parameter for monitoring the outcomes of patients suffering from GTN, shows a significant decrease after both surgical treatments (curettage and hysterectomy), and after the application of chemotherapy. It is noticed that therapeutic effect is better after the application of chemotherapy with regard to operative treatment in patients who had underwent hysterectomy and that surgical treatment is necessary to combine with chemotherapy. In the treatment of non-metastatic trophoblastic disease, chemotherapy alone is usually very successful (12,14).

Follow up

Hydatiform mole

After evacuation of the mole, all the patients must be monitored for determination of hCG value so that remission of disease could be confirmed with certainty. The values of serum hCG after a normal pregnancy become immeasurable after two weeks. It is believed that about 80% of patients come to spontaneous regression of hCG levels after the evacuation of the mole. The mean time for reaching the immesurable values is 73 days. In 2% of cases there is regression in the first ten days after the evacuation. However, it may take up to six months, during which the value of hCG slowly declines and returns to normal values.

hCG values are determined every two weeks until reaching two consecutive negative titres, and after that the control should be done in a month, until the expiration of one year from the evacuation of the mole. If the values are negative, the interval between the control can be extended to two months.

Physical examination is necessary to perform two weeks to achieve remission, and thereafter every three months to the end of the monitoring period. The first sample for testing the value of hCG should be taken one week after the mole evacuation. After the initial chest X-ray examination, re-recording should be done only if hCG shows a plateau or increase. In patients who had mole, 6-12 weeks after each subsequent pregnancy the level of hCG should be determined because of the risk of choriocarcinoma which is present in these women. The patient in whom hCG levels do not fall to normal after eight weeks of evacuation should be monitored for two years. When negative titar of hCG is reached in the first year, this marker should be monitored for a month in the first, and three months in the second year.

Chemotherapy should begin immediately if:

1) hCG titre shows a plateau or increase

2) at any time during the follow-up if metastasis is detected.

Gestational trophoblastic neoplasia

Because of potential danger of choriocarcinoma relapse after few years, it is necessary to provide life-long monitoring of patients treated for gestational trophoblastic tumors, when the frequency of monitoring gradually decreases.

Quantitative determination of hCG levels in serum should be done monthly during the first six months, then every other month until the end of the first year, every three months during the second two years and six months of the expiry of the second year after treatment.

Relapses during the first three months are rather the consequence of disease persistence than of recurrence, while the real relapse occurs during the first year of treatment. Healing is considered complete if the disease does not appear again for a period of five years of treatment.

Contraception should be maintained over one year after completion of chemotherapy. Barrier methods of contraception and oral contraceptives are acceptable, however, priority is given to oral contraceptives because they perform suppression of pituitary hormons that can interfere with accurate measuring of hCG.

In further pregnancies, it is necessary to do ultrasound examination during the first trimester to determine the development of normal gestation, because of the patient with increased risk of gestational trophoblastic disease in the next pregnancy. Also, the products of conception or placenta in future pregnancies should be examined histologically, and the level of hCG followed for six weeks and three months after the end of pregnancy (15,16).

Reproduction

Successful chemotherapeutic treatment of GTN has enabled a large number of women that, despite exposure to drugs that have teratogenic properties, to preserve their reproductive potential. 83% of successful pregnancies was noted in this group of patients, and, according to Woolas, there is no difference between those who received a single agent and combined chemotherapy (17). Also, in these patients, the incidence of abortion, stillbirth, congenital anomalies, prematurity or larger opstetric complications was not increased. However, it is advisable to delay pregnancy for one year after chemotherapy in patients with GTN and low risk and two years for those at high risk, because of theoretical risk of teratogenic effect of chemotherapy (14). Delaying pregnancy allows DNA repair and eventual apoptosis of damaged ovarian cells. Studies have shown that female patients treated with chemotherapy enter menopause with 45 years of age (18).

Later malignancy

Because many anticancer drugs are known as carcinogens, there is a belief that chemotherapy used to induced a long-term remission or cure a cancer can lead to the occurrence of another malignancy (19). There was no confirmation of the existence of increased tendency for the occurrence of second malignancy after successful treatment of trophoblastic tumors, probably because of relatively short exposure of these patients to chemotherapy and rare implementation of alkilic drugs (20).

By the implementation of the best of the knowledge acquired and experience, not a single life should be lost for gestational trophoblastic disease (18, 21).

Conclusion

Until the mid-fifties of the 20th century, when Li et al. described the first complete and prolonged remission in patients with choriocarcinoma treated with methotrexate, prognosis of these diseases was very bad, even fatal in 90-95% of cases. Since then, owing to the knowledge acquired and experience GTN was classified among the most successfully treated gynecological malignancies (22). Very good response to chemotherapeutics, acute tolerance and cumulative doses of the same, makes this the treatment of first choice.

Using the experience gained so far, not a single life should be lost for gestational trophoblastic disease..

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LEČENJE GESTACIJSKIH TROFOBLASTNIH BOLESTI

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Gestacijske trofoblastne bolesti su neoplazme trofoblasta i stanja koja su predispozicija za neoplazmu. To su: hidatiformna mola (kompletna i parcijalna), invazivna mola, gestacijski horiokarcinom i trofoblastni tumor placentnog ležišta. U skladu sa kriterijumima i preporukama Svetske zdravstvene organizacije (WHO) i Internacionalnog udruženja za ginekologiju i akušerstvo (FIGO) vrši se klasifikacija i stratifikacija bolesti, na osnovu čega se sprovodi lečenje po već utvrđenim protokolima. Benigne forme se leče hirurški, dok je kod malignih, terapija izbora hemioterapija - jedan hemioterapeutik kod nemetastatske bolesti sa niskim rizikom ili kombinacija hemioterapeutika kod visoko rizičnih metastatskih formi. Sa odgovarajućim protokolom, stepen preživljavanja je 100% u grupi bolesnica sa niskim skorom, odnosno 80% sa visoko rizičnim skorom. Primenom do sada najboljih stečenih znanja i iskustava ne sme se dozvoliti da život i jedne žene bude izgubljen zbog gestacijskih trofoblastnih bolesti. *Acta Medica Medianae 2010;49(1):64-69.*

Ključne reči: *hemioterapija, gestacijske trofoblastne bolesti, radijaciona terapija, hirurška terapija*