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Treating cancer with high temperatures: whole-body hyperthermia as promising strategy to enhance antitumor efficacy of multimodal treatment for malignant tumor.

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Abstract

In this article, the author report on the method of Whole-Body Hyperthermia (WBH) and its capabilities in the treatment of patients with malignant tumors. The authors indicate good tolerability and high efficiency of WBH in the treatment of patients with renal cell carcinoma, disseminated melanoma, soft tissue sarcomas and retroperitoneal space.

Keywords: High temperature, Whole-body hyperthermia, Malignant tumors.

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Introduction

A well-known fact is that the main methods of treatment of malignant tumors are surgical intervention, chemotherapy and radiotherapy. These methods are used in the schemes of combined and complex treatment. Combined treatment is based on the use of one-way treatment in one patient (for example, a surgical intervention followed by a course of radiotherapy or chemotherapy). Complex treatment is based on the use of local and systemic methods of affecting the tumor (surgical interventional and systemic chemotherapy). There is also a combined method of treatment, which is based on the simultaneous use of the same methods with different mechanisms of action (for example, a combination of remote and interstitial radiation therapy).

One of the current and effective directions of antitumor treatment is multicomponent (multimodal) treatment. Multimodal treatment is understood as complex therapy, which is supplemented by the use of methods that significantly modify the sensitivity of malignant tumors to chemotherapy and radiotherapy. As the modifiers that selectively enhance the sensitivity of tumor cells to chemotherapy and/or radiation therapy, various physicochemical effects are used: Hyperbaric oxygenation, peroxides, local and general hypoxia, electron-withdrawing compounds, artificial hyperglycemia, ultrasound, persistent magnetic fields, laser beams, photodynamic therapy.

One of the most interesting areas of scientific and clinical research is the use as a modifying agent of a method such as whole-body high-frequency electromagnetic hyperthermia (WBH). The starting point for research in this area is the features of the micro physiology of tumor tissue, which distinguish it from normal. Such features are active glycolysis, low value of pH, active glycolysis, presence of hypoxia zones in the tumor and slow blood flow. These properties of tumor tissue are a prerequisite for the development of new methods of treatment of malignant tumors based on the use of selective effects on the tumor [1,2].

In the world literature, the term «hyperthermic oncology» are used, which denote a relatively new direction in the treatment of malignant tumors that has been developing rapidly during the past 20-25 years, associated, as already indicated, with the use of high temperature (40-42.5°C at the general influence and/or 42-47°C at local) for increase of efficiency of the combined or complex therapy of oncological patients. In recent years more than 25,000 patients with these forms of malignant tumors have been treated at scientific centers in USA, Japan, Germany, Italy, Netherlands, Russian Federation and Belarus. Inclusion of WBH in combined and complex treatment regimens allows increasing the antitumor effectiveness of therapy of patients with malignant tumors of mammary gland, lung, esophagus, liver, pancreas, cervix, kidneys and prostate. The obtained results indicate an increase in the antitumor efficacy of treatment of patients with these nosological forms of malignant tumors more than 1.5-2.5 times when included in the combined and complex treatment of WBH [1-3].

Opportunities and Clinical Results of N.N. Alexandrov National Cancer Center

One of the leading scientific oncological centers involved in the study of antitumor efficacy of WBH in Europe and Eurasia is N.N. Alexandrov National Cancer Center (Lesnoy, Republic of Belarus). At the moment, more than 2000 patients with malignant tumors have been treated at the Department of Hyperthermia and Photodynamic Therapy of this Center with use of the system for high-frequency electromagnetic hyperthermia («Ptich M», Faculty of Radio physics and Computer Technologies, Belarusian State University, Republic of Belarus, 13.56 MHz).

The main indications for the use of WBH are:

1. Unrespectable forms of tumors with the purpose of their translation as a result of regression into a resectable state.
2. Generalized forms of malignant neoplasms, in which traditional methods of treatment are ineffective or seemingly unpromising.
3. Malignant tumors, which in the course of treatment

developed resistance to cytostatic therapy (chemo- and radio resistant tumors).

4. Non-radical or conditionally radical surgery.

WBH in the form of thermo-chemotherapy, thermo-radiotherapy and thermo-radio-chemotherapy is currently used in the treatment of patients with different forms of malignant tumors, namely:

1. Skin melanoma (stage III/IV, relapses and metastases after radical treatment).
2. Renal cell carcinoma in the presence of distant and regional metastases).
3. Soft tissue sarcomas (stage III/IV, relapses and metastases after radical treatment).
4. Bone sarcomas (stage III/IV, relapses and metastases after radical treatment).
5. Inorganic tumors of the retroperitoneal space.
6. Unrespectable cervical cancer.
7. Chemo resistant ovarian tumors.

The session of WBH is a multi-stage process and can be conditionally divided into the following stages.

Preparatory stage

At this stage, the patient is prepared to perform WBH session, patient is admitted to anesthesia, temperature sensors are calibrated, subclavian vein is catheterized for infusion of liquids and medications. To prevent infectious complications (*Herpes labialis*) at this stage, intravenous drip infusion of Acyclovir in a dose of 5 mg/kg.

Stage of middle hyperthermia (up to 40°C)

The hyperthermic unit is turned on (Figure 1), patient's body is heated to 40°C, infusion of 250-500 ml of physiological solution and 5000 units of heparin and antiulcer drug is performed, an intravenous injection of 40% glucose in a dose of 3.25 mg/kg for 30 min is performed with the goal of creating hyperglycemia at a level of 20-33 mmol/l.

The main technical advantages of «Ptich M» are small-size generator with automatic matching device, 6 channels of temperature measurement (accuracy ± 0.1°C), automatic control of high-frequency radiation power, multi-channel modular system for monitoring the temperature of heated areas of the body and visual/audible alarms for emergency situations.

Stage of high hyperthermia (more than 40°C)

This stage is the main stage of hyperthermia. Its duration is 2.5-4 h. When the maximum temperature (41.8-42.5°C) is reached, intravenous infusion of chemotherapy drugs is performed during 1 h. The monitoring of the state of the water-electrolyte balance and the state of the cardiovascular system is continuing.

Cooling stage

At this stage, infusion of drugs necessary to maintain the water-electrolyte balance is stopped. The patient is withdrawn from anesthesia and transported to the intensive care unit.

All the adverse reactions and complications that were detected during the WBH sessions were:

Early complications

Dyspeptic disorders (nausea, vomiting, diarrhea); hemodynamic disorders (falling diastolic blood pressure, sinus arrhythmia, tachycardia) and late complications: hematologic disorders

Figure 1. *Apparatus for whole-body high-frequency electromagnetic controlled hyperthermia «Ptich M» (the device is designed for Faculty of Radiophysics and Computer Technologies, Belarusian State University, Republic of Belarus).*

(anemia, leukopenia and thrombocytopenia); undesirable reactions of the phenomenon from the kidneys (increase in creatinine to 150-190 μmol/l, proteinuria to 1 g/l); alopecia; temperature damage to the skin and subcutaneous tissue manifest themselves as painful indurates and viral diseases (herpes). All reactions corresponded to I to III degrees according to CTCAE (Version, 4.0., 2009). Based on analysis of data on the incidence and severity of adverse reactions that occurred during WBH sessions, we concluded that the method of treatment is well tolerated and safe.

In N.N. Alexandrov National Cancer Center has accumulated a serious experience of using WBH in the treatment of soft tissue sarcomas, disseminated skin melanoma, renal cell carcinoma of the skin and tumors of the retroperitoneal space.

Thus, the use of WBH (41.5-42°C; 60-90 min.) patients (n=306) with for soft tissue sarcomas in combination with local hyperthermia and surgical intervention and chemotherapy significantly increased the indices of 3 and 5-year survival in comparison with the groups «surgery», «surgery + radiotherapy» and «surgery+chemotherapy». The 3-year survival rates were 77.2 ± 6.7; 59.2 ± 8.2; 61.0 ± 6.4 and 61.4 ± 2.8% ($p<0.05$). The 5-year survival rates were 74.3 ± 7.0; 40.0 ± 8.5; 51.8 ± 6.6 and 50.8 ± 7.1% ($p<0.05$).

In patients with resectable distant metastases of renal cell carcinoma (n=35), which underwent a radical surgery at the first stage, and after the operation, WBH (41.8-42°C; 60-90 min.) with hyperglycemia (22-33 mmol/l) and chemotherapy with doxorubicin 60 mg/m^2 after interferon-alpha injection, we marked a significant increase in survival rates. The parameters of 3 and 5-year survival in this group compared with the group «surgery» (n=54) and «surgery + WBH without interferon-alpha» (n=36) were 65.0 ± 8.2; 43.4 ± 6.7; 46.0 ± 8.4% ($p<0.05$) and 53.8 ± 9.0; 32.6 ± 6.6; 39.9 ± 8.3% ($p<0.05$), respectively.

In another study, the use of WBH (41.8-42°C; 60-90 min.) with adriamycin (50 mg/m^2) chemotherapy and hyperglycemia (22-33 mmol/l) (n=58) performed after surgery allowed to increase the 3-year survival from 31.4 ± 8.8 (in the «surgery» group, n=42), 42.8 ± 8.3 (in the group «radiation therapy 14 Gy + surgery», n=41) to 66.4 ± 7.3% ($p<0.05$). There was also an increase in 3 and 5-year survival in patients with metastases in regional lymph nodes after WBH sessions with hyperglycemia and chemotherapy compared to groups «surgery» and «radiation therapy 14 Gy + surgery»: 60.9 ± 10.4; 10.8 ± 7.9 and 20.8 ± 10.6%, respectively ($p<0.05$) and 60.9 ± 10.4; 5.4 ± 3.8 and 10.4 ± 7.6%, respectively ($p<0.05$).

The use of WBH (2 sessions 41-42.5°C; 60-90 min with an interval of 3-6 weeks) with hyperglycemia (22-33 mmol/l) and chemotherapy with doxorubicin (50 mg/m^2) and cisplatin (90-100 mg/m^2) in 122 patients with low-grade sarcomas of the retroperitoneal space increased the 1, 2 and 3-year survival rates compared with standard treatment regimens: from 53.0 ± 6.6 to 88.0 ± 6.1%, from 29.9 ± 6.3 to 49.3 ± 9.3 and from 16.1 ± 5.3 to 26.6 ± 8.2% respectively ($p<0.05$).

According to our data, the use of 3-6 sessions of WBH (41.8-42.5°C; 60-90 min.) with dacarbazine (60 mg/m^2) and hyperglycemia (22-33 mmol/l) in patients with disseminated melanoma (stage III) with metastases of regional lymph nodes allows to achieve a 5-year survival rate of 53.1%, which is 2 times higher than in the standard treatment group. In patients with stage IV of the disease (the presence of metastases in the skin, subcutaneous tissue, internal organs, etc.) the application of the above treatment allows to achieve a 10-year survival rate of 24.7 ± 8.5%. As a rule, with the use of chemotherapy and immunotherapy without WBH with this stage of the disease, all patients die within 2 years.

The results demonstrated by us testify to the high antitumor efficacy of the WBH method when included in multimodal treatment regimens in patients with a number of nosological forms of malignant tumors.

Conclusion

1. WBH is safe and well tolerated method in the treatment of patients with malignant tumors III-IV stages and is accompanied by a relatively low incidence of adverse reactions and complications. As a rule, the arising reactions correspond to I-III degrees (according to CTCAE, version 4.0., 2009).
2. WBH is a highly effective method of treating patients with generalized forms of malignant tumors, in which traditional methods of treatment are ineffective or seemingly unpromising, unresectable forms of tumors with the purpose of their translation as a result of regression into a resectable state, non-radical or conditionally radical surgery and malignant neoplasms, which in the course of treatment developed resistance to cytostatic therapy (chemo- and radioresistant tumors).
3. The use of WBH in schemes of complex treatment of patients with malignant tumors (soft tissue sarcomas, skin melanoma, bone sarcomas, renal cell carcinoma, and breast cancer, inorganic tumors of the retroperitoneal space, unresectable cervical cancer, chemoresistant ovarian tumors and other) allows to significantly increasing the antitumor efficacy of chemotherapy and radiotherapy.

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