

The algorithm of the pathogenetic treatment of primary and metastatic melanoma includes three drugs: disulfiram (drops, tablets, sterile pellets (Esperal), ampoules), CuSO_4 (drops) and ZnSO_4 (zinc ointment, tablets).

Excellent antitumoral effects of these three drugs against melanoma in vitro and in vivo were presented in articles and patents [9-38].

1: Patients with a primary melanoma T1-4N0-3M0 stage.

- a) Before operation: During 2-4 weeks a patient receives a local treatment (disulfiram plus CuSO_4 – drops) and systemic treatment [disulfiram (250-500 mg/day) plus zinc sulfate (45-90 mg chelated elemental Zn^{2+} – thrice daily)] for decrease of melanoma cells activity.
- b) In the end of operation a patient receives a local treatment (Esperal is a sterile pellets of disulfiram for subcutaneous or intramuscular implantation – 100-800 mg (100 mg * 2 x 4 = 800 mg) depending on anatomic location and radical radial margin of surgical skin excision) for a future decrease of melanoma cells activity and formation of local relapse [32].
- c) After operation during 1-6 months (maximal period may make up 5 years) a patient can receive a partial local pathogenetic treatment (disulfiram plus CuSO_4 – drops) and/or a systemic pathogenetic treatment [disulfiram (250-500 mg/day) plus zinc sulfate (45-90 mg chelated elemental Zn^{2+} – thrice daily)] for decrease of risk of melanoma metastases.

2: Patients with metastatic melanoma N1-3.

- a) Before operation: During 2-4 weeks a patient receives a systemic treatment [disulfiram (250-500 mg/day) plus zinc sulfate (45-90 mg chelated elemental Zn^{2+} – thrice daily)] for decrease of melanoma cells activity.
- b) In the end of operation a patient receives a local treatment (if it is possibly – Esperal is a sterile pellets of disulfiram for subcutaneous or intramuscular implantation – 100-800 mg (100 mg * 2 x 4 = 800 mg) depending on anatomic location and radical radial margin of surgical skin excision) for a future decrease of melanoma cells activity and formation of local relapse [32].
- c) After operation during 1-6 months (maximal period may make up 5 years) a patient can receive a systemic pathogenetic treatment [disulfiram (250-500 mg/day) plus zinc sulfate (45-90 mg chelated elemental Zn^{2+} – thrice daily)] for decrease of risk of melanoma metastases.

3: Patients with metastatic melanoma M1a.

- a) Before operation: During 2-4 weeks a patient receives a systemic treatment [disulfiram (250-500 mg/day) plus zinc sulfate (45-90 mg chelated elemental Zn^{2+} – thrice daily)] for decrease of melanoma cells activity. If it is possibly a patient receives a local treatment (disulfiram plus CuSO_4 - drops) for decrease of melanoma cells activity.
- b) In the end of operation a patient receives a local treatment (if it is possibly – Esperal is a sterile pellets of disulfiram for subcutaneous or intramuscular implantation – 100-800 mg (100 mg * 2 x 4 = 800 mg) depending on anatomic location and radical radial margin of surgical skin excision) for a future decrease of melanoma cells activity and formation of local relapse.
- c) After operation during 1-6 months (maximal period may make up 5 years) a patient can receive a systemic pathogenetic treatment [disulfiram (250-500 mg/day) plus zinc sulfate (45-90 mg chelated elemental Zn^{2+} – thrice daily)] for decrease of risk of melanoma metastases.

4: Patients with metastatic melanoma M1b-c [11].

- a) During 5 years a patient can receive a systemic pathogenetic treatment [disulfiram (250-500 mg/day) plus zinc sulfate (45-90 mg chelated elemental Zn^{2+} – thrice daily)] for decrease of melanoma metastases and for increase of survival. Also, for intratumoral treatment may be used the liquid form of disulfiram (disulfiram long – ampoules) [22].

This algorithm of the pathogenetic treatment may help to decrease mortality and may help to increase a survival of patients with melanoma. Probably it will help to raise the 5 years survival rate up to 50 % in the patients with secondary metastatic melanoma.

Clinical cases of the pathogenetic treatment of patients with primary and metastatic melanoma

Case 1. Local treatment of primary melanoma with disulfiram (drops) and CuSO₄ (drops) during a short time (from October 2006 to January 2007)

A 42-year-old woman presented in March 2005 with melanoma (T4(?)N0M0; Breslow thickness, 4-5 mm) on the left cheek (Fig. 1a). Primary size was 25*22 mm, estimated area of excision is 45*43 mm. Melanoma was confirmed cytologically. No lymph node or visceral metastases were found after staging procedures (x-ray of the thorax and sonography of the abdomen and the regional lymph nodes) were performed [1-6].



Fig. 1. Clinical effects of local treatment of patient with melanoma of left cheek (case 1). Primary size was 25*22 mm. Thickness of melanoma above skin was 4-5 mm. Breslow thickness was 4-5 mm. [a]. In March 2005, treatment with polyantigenic xenogenic antitumor vaccine (PAXAV) was started. In July 2005, clinical effect was stable disease. [b]. In July 2005, local active immunotherapy by means of IL-2 was started. In November 2005, clinical effect was minimal response. [c]. In October 2006, local pathogenetic treatment with disulfiram (drops) and CuSO₄ (drops) was started. In January 2007, after 2.5 months of local pathogenetic treatment with disulfiram (drops) and CuSO₄ (drops) the clinical effect was complete response. Skin of left cheek is clean. [d]. In December 2009, in June 2011, in June 2012 and in June 2013, skin of left cheek is clean.

This localization of large melanoma has a high risk of local and distant relapse (recurrences) after operation.

In March 2005, treatment with polyantigenic xenogenic antitumor vaccine (**PAXAV**) was started (**Fig. 1a**). **In July 2005**, **clinical effect** was **stable disease** [7, 8].

In July 2005, local active immunotherapy by means of IL-2 was started.

In November 2005, **clinical effect** was **minimal response** (**Fig. 1b**).

In November 2005, treatment with polyantigenic xenogenic antitumor vaccine (**PAXAV**) plus BCG was started [7]. **In October 2006**, **clinical effect** was **minimal response** (**Fig. 1b**).

In October 2006, **local pathogenetic treatment** (**disulfiram plus CuSO₄ – drops**) was started [9-38]. **In January 2007**, after 2.5 months of local pathogenetic treatment (**disulfiram plus CuSO₄ – drops**) the clinical effect was **complete response** (**Fig. 1c**).

In December 2009, in June 2010, in June 2011, in June 2012, and in June 2013, skin of left cheek is clean (**Fig. 1d**).

No lymph node or visceral metastases were found after staging procedures (x-ray of the thorax and sonography of the abdomen and the regional lymph nodes) were performed.

Treatment of primary melanoma was without surgery, chemotherapy and X-ray therapy.

Treatment of this patient demonstrates the possibility of local treatment of large primary melanoma (**disulfiram plus CuSO₄ – drops**) in problem localizations [9-38]. If there is a possibility of local treatment of large primary melanoma in problem localizations, hence there is a possibility of local treatment in other localizations without surgery, chemotherapy and X-ray therapy.

The presumable results of treatment efficacy (complete regressions) may be: 100% for size < 1.0 cm, 95% for size from 1.0 to 2.0 cm, 80-90% for size > 2.0 cm.

Risk for local recurrence of melanoma head/neck is 9.4 (table No. 3 in: Balch CM et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1-4 mm melanomas. *Ann Surg Oncology* 2001; **8(2)**: 101-108 [2]).

In this case there is the possibility to create new forms of drugs.

Case 2.

Local treatment of secondary metastatic melanoma with zinc ointment

A 63-year-old woman presented **in August 2001** with a malignant melanoma (**T3N0M0; Clark level IV; Breslow thickness, 5-6 mm**) on her right shin of leg (posterior region of leg), which was initially treated with wide excision [1-6].

In June 2003, several skin lesions of metastatic melanoma were noted on the right shin of leg (posterior region of leg). Multiple new skin-colored, brownish red, and **dark blue smooth-surfaced and eroded papules and nodules** of metastatic melanoma appeared on the whole right lower leg **in June 2003** (**Fig. 2a**). There was an unresectable form of secondary metastatic melanoma.

A **large ulcerated nodule** (1.8 cm in diameter) was noted on the right posterior crural region (**Fig. 2a**). Metastatic melanoma was confirmed cytologically.

No lymph node or visceral metastases were found after staging procedures (x-ray of the thorax and sonography of the abdomen and the regional lymph nodes) were performed.

In June 2003, treatment with **polyantigenic xenogenic antitumor vaccine (PAXAV)** was started [7, 8].

In October 2003, clinical effect was **stable disease**.

In October 2003, local active immunotherapy by means of IL-2 was started and was finished **in February 2004**. Clinical effect was **minimal response** (**Fig. 2b**).

In February 2004, **local partial pathogenetic treatment** (**zinc ointment**) and **PAXAV** plus IL-2 were started.

In January 2006, clinical effect was **partial response** (**Fig. 2c**).

No lymph node or visceral metastases were found after staging procedures (x-ray of the thorax and sonography of the abdomen and the regional lymph nodes) were performed.

Treatment of **metastatic melanoma** was **without surgery, chemotherapy and X-ray therapy**.

Treatment of this patient demonstrates the possibility of use of **local partial pathogenetic treatment** (**zinc ointment**) in patients with secondary metastatic melanoma (multiple metastases in skin).

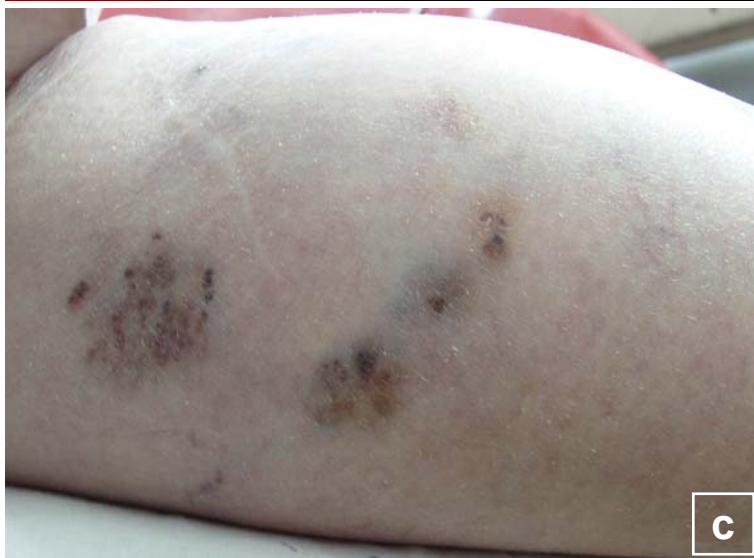


Fig. 2. Clinical effects of local treatment (zinc ointment) of patient (case 2) with metastatic melanoma of right shin of leg (posterior region of leg).

[a] Right shin of leg (posterior region of leg) showing multiple papules and an ulcerated nodule of cutaneous melanoma metastases (**black circumferences**).



[b] Right shin of leg (posterior region of leg) with multiple cutaneous melanoma metastases (**dark blue smooth-surfaced papules and nodules**) after 5 months of treatment with local active immunotherapy by means of IL-2, multiple cutaneous melanoma metastases are minimally decreased. Clinical effect was **minimal response**.



[c] Right shin of leg (posterior region of leg) with multiple cutaneous melanoma metastases (**skin-colored and brownish red smooth-surfaced papules**) after local partial pathogenetic treatment (**zinc ointment**). Clinical effect was **partial response**.

Case 3. Treatment of metastatic melanoma with disulfiram (tablets) and zinc sulfate (tablets) during a long time (from October 2006 to September 2013)

A 42-year-old woman presented **in May 2001** with melanoma (**T2N0M0; Clark level III**) on her back, which was initially treated with wide excision (**Fig. 3a**) [1-6].

In July 2002, local melanoma metastases were noted in lymph nodes of a left axillaries region (N3), which was treated with wide excision (**Fig. 3b**). Metastatic melanoma was confirmed histopathologically. It was a **first relapse**.

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Fig. 3. Patient 3 with metastatic melanoma of back.

[a] In May 2001, postoperative scar on back.

[b] In July 2002, postoperative scar of a left axillaries region.

[c] In April 2003, postoperative scar of a left axillaries region.

In March 2004, complete regression of solitary melanoma metastasis

In March 2003, regional nodal metastases of melanoma were noted in the postoperative scar of a left axillaries region (N3), which was treated with wide excision (Fig. 3c). Metastatic melanoma was confirmed histopathologically. It was a second relapse.

In May 2003, treatment with polyantigenic xenogenic antitumor vaccine (PAXAV) was started [7, 8].

In October 2003, clinical effect was progression of disease. Multiple (innumerable) metastases (6-36 mm) of melanoma were noted in lymph nodes of a left axillaries region and solitary melanoma metastasis (40*17 mm) was noted in the postoperative scar (N3). It was a third relapse.

In October 2003, treatment with mixed vaccine (PAXAV plus BCG) and local active immunotherapy by means of IL-2 were started [7]. In January 2004, clinical effect was minimal response.

In March 2004, complete regression of solitary melanoma metastasis was noted in the postoperative scar after local mixed vaccine (PAXAV plus BCG) therapy (Fig. 3c).

From March 2004 to April 2005, partial regression of multiple metastases of melanoma (decrease of sizes and quantity of metastases) were noted in lymph nodes of a left axillaries region.

From March 2005 to January 2006, a decrease of metastases quantity of multiple metastases of melanoma (7 lymph nodes) was noted in lymph nodes of a left axillaries region. Clinical effect was minimal response.

In April 2006, multiple distant hypoechogenic lymph nodes (neck, region of pancreas, inguinal lymph node – multiple melanoma metastases M1a – ?) were noted during usual mixed vaccine (PAXAV plus BCG) and interferon alpha therapy. It was a fourth relapse.

In April 2006, treatment with mixed vaccine (PAXAV plus BCG) was stopped and another therapy was started. In October 2006, clinical effect was complete (inguinal lymph node) and partial (neck, region of pancreas) regression of multiple melanoma metastases M1a (?).

In October 2006, pathogenetic treatment with disulfiram (500 mg/day) plus zinc sulfate (ZnSO_4 – 45 mg chelated elemental Zn^{2+} – thrice daily) was started [9-38].

In April 2007, clinical effect was complete regression of hypoechogenic lymph nodes in region of pancreas and neck.

From April 2007 to August 2010, complete regression of multiple melanoma metastases (3-6 mm) was noted in lymph nodes of a left axillaries region.

Unfortunately, this patient has only a very slow regression, but she lives (September 2013).

Treatment of metastatic melanoma was without surgery, chemotherapy and X-ray therapy.

Treatment of this patient demonstrates the possibility of use of systemic pathogenetic treatment [disulfiram (250-500 mg/day) plus zinc sulfate (ZnSO_4 – 45-90 mg chelated elemental Zn^{2+} – thrice daily)] of patients with secondary metastatic melanoma (multiple metastases in lymph nodes). The presumable results of treatment efficacy (complete and partial regressions) may be 50-70%.

But there is the possibility of local and systemic pathogenetic treatment of patients with a primary melanoma T1-4N0-3M0, stage III [9-38].

Also, there is the possibility of intratumoral pathogenetic treatment (liquid form of disulfiram [disulfiram long] (ampoules) plus zinc sulfate – tablets – 45 mg chelated elemental Zn^{2+} – thrice daily) of patients with subcutaneous metastases or intrahepatic metastases.

This algorithm of the pathogenetic treatment may help to decrease mortality and may help to increase a survival of patients with melanoma.

Probably it will help to raise the 5 years survival rate up to 50 % in the patients with secondary metastatic melanoma

- fig. 1 and fig. 2 in: Balch CM et al. Ann Surg Oncology 2001; 8(2): 101-108;
- fig. 1 and fig. 2 in: Balch CM et al. J Clin Oncol 2009; 27(36): 6199-206;
- fig. 1 in: Balch CM et al. J Clin Oncol 2010; 28: 1-9 [2, 5, 6].

This algorithm of pathogenetic treatment of primary and metastatic melanoma with disulfiram (drops, tablets, sterile pellets (Esperal), ampoules), CuSO_4 (drops) and ZnSO_4 (zinc ointment, tablets) may be very simple and very effective.

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