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.

Web-site: http://www.drturumin.com
e-mail: drjacobturumin@yahoo.com

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].

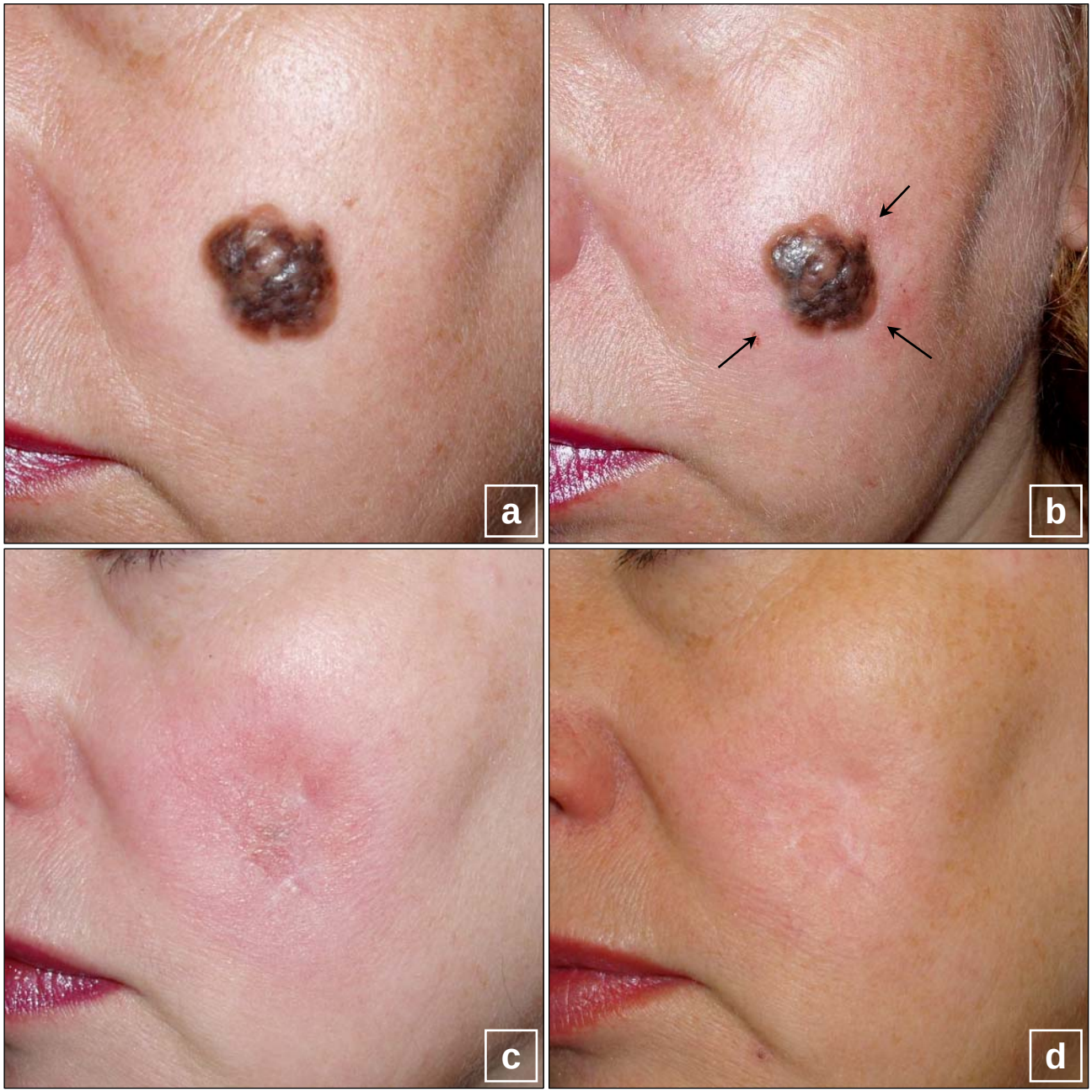


Fig. 1. Clinical effects of local treatment of patient with **melanoma of left cheek** (**case 1**). **Primary size** was **25*22 mm**. **Thickness of melanoma above skin** was **4-5 mm**. **Breslow thickness** was **4-5 mm**. **[a]. In March 2005,** treatment with **polyantigenic xenogenic antitumor 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 $CuSO_4$ (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 $CuSO_4$ – drops**) was started [9-38]. **In January 2007,** after 2.5 months of local pathogenetic treatment (**disulfiram plus $CuSO_4$ – 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 $CuSO_4$ – 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**).

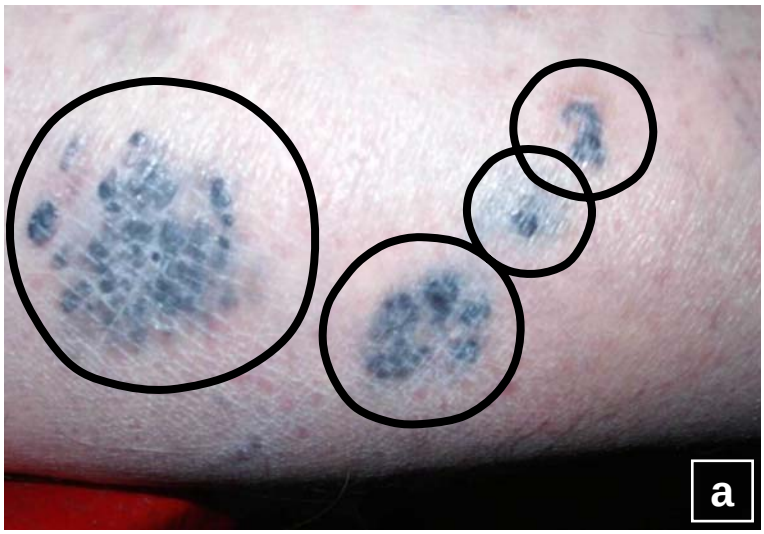
In February 2004, local partial pathogenetic treatment (**zinc ointment**) and **PAXAV** plus IL-2 were started.

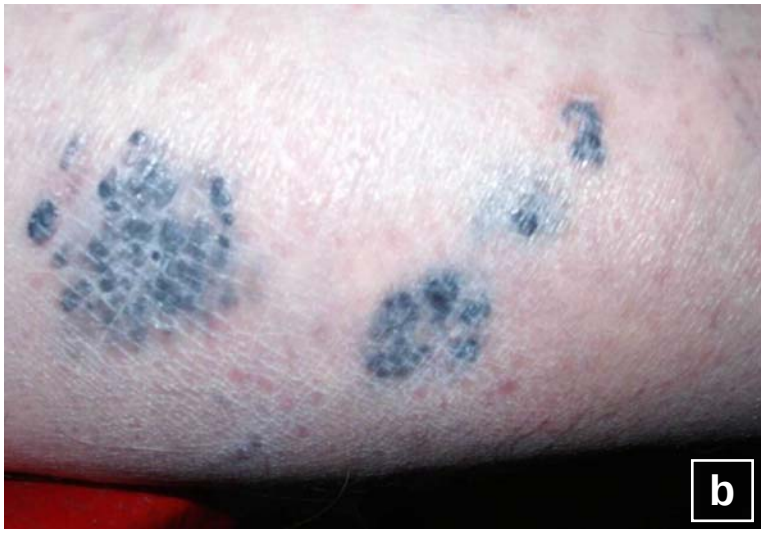
In January 2006, clinical effect was **partial response** (**Fig. 2c**).

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).





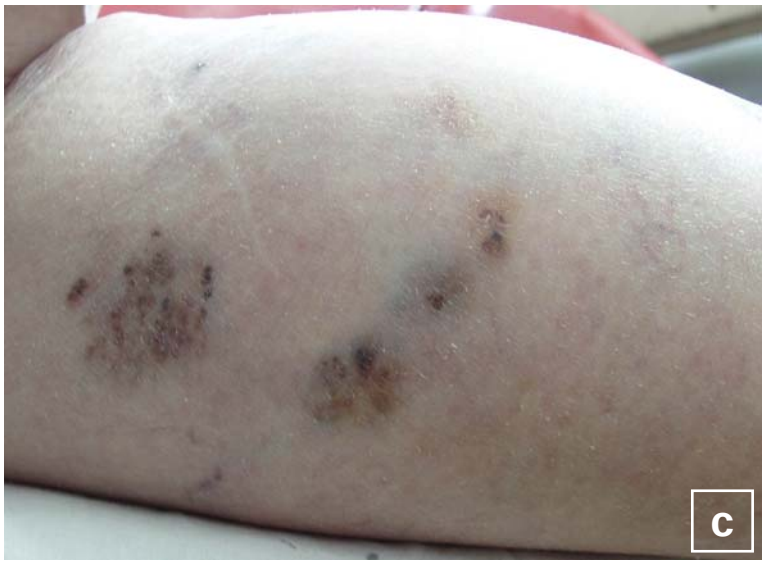


Fig. 2. Clinical effects of local treatment (zinc ointment) of patient (case 2) with metastatic melanoma of right shin of leg (posterior region of leg).

[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**.

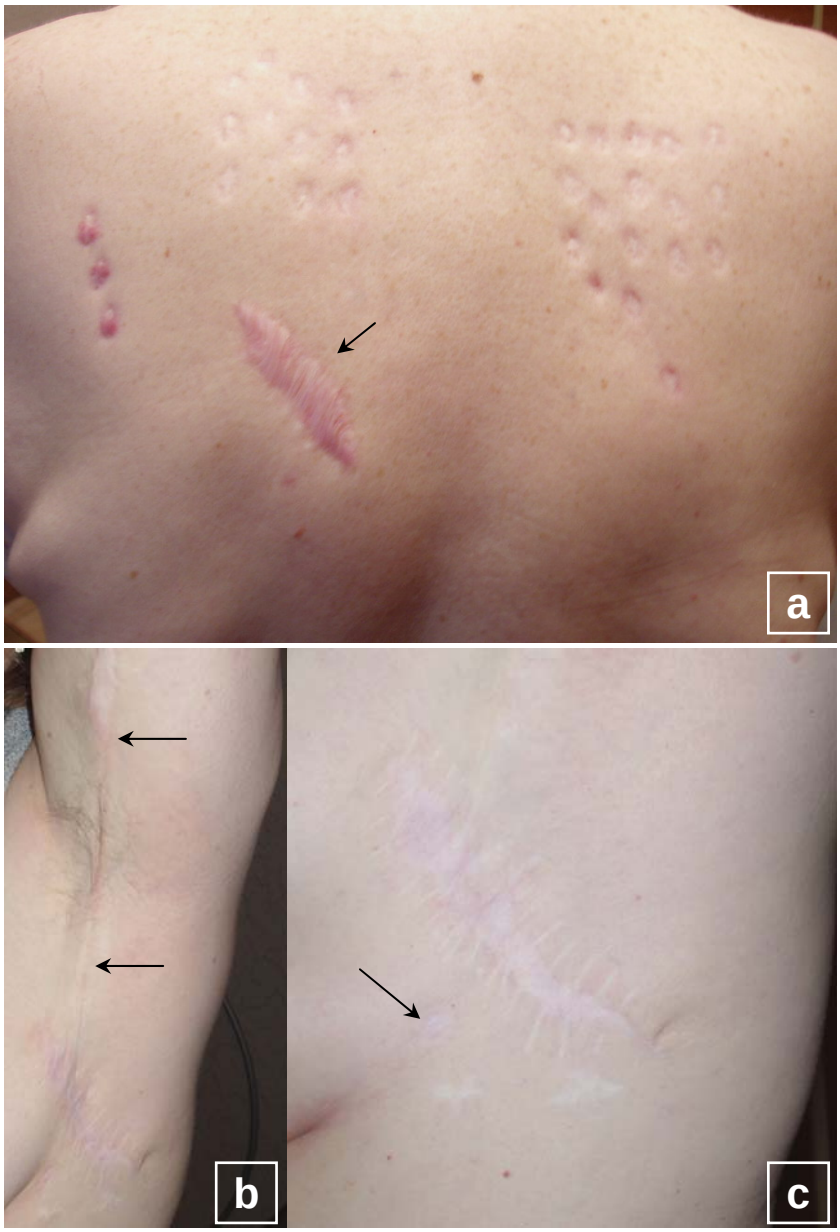


Fig. 3. Patient 3 with metastatic melanoma of back.

[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.

References (Staging System for Cutaneous Melanoma):

1. Balch CM, Buzaid AC, Soong SJ, Atkins MB, Cascinelli N, Coit DG, Fleming ID, Gershenwald JE, Houghton AJr, Kirkwood JM, McMasters KM, Mihm MF, Morton DL, Reintgen DS, Ross MI, Sober A, Thompson JA, Thompson JF. Final Version of the American Joint Committee on Cancer. *J Clin Oncol* 2001; **19(16)**: 3636-3648.
2. Balch CM, Soong SJ, Smith T, Ross MI, Urist MM, Karakousis CP, Temple WJ, Mihm MC, Barnhill RL, Jewell WR, Wanebo HJ, Desmond R. Long-Term Results of a Prospective Surgical Trial Comparing 2 cm vs. 4 cm Excision Margins for 740 Patients With 1-4 mm Melanomas. *An Surg Oncol* 2001; **8(2):** 101-108.
3. Balch CM, Soong SJ, Ross MI, Urist MM, Karakousis CP, Temple WJ, Mihm MC, Barnhill RL, Jewell WR, Wanebo HJ, Harrison R. Long-Term Results of a Multi-Institutional Randomized Trial Comparing Prognostic Factors and Surgical Results for Intermediate Thickness Melanomas (1.0 to 4.0 mm). *An Surg Oncol* 2000; **7(2)**: 87-97.
4. Balch CM, Soong SJ, Atkins MB, Buzaid AC, Cascinelli N, Coit DG, Fleming ID, Gershenwald JE, Houghton AJr, Kirkwood JM, McMasters KM, Mihm MF, Morton DL, Reintgen DS, Ross MI, Sober A, Thompson JA, Thompson JF. An Evidence-based Staging System for Cutaneous Melanoma. *CA Cancer J Clin* 2004; **54(3)**:131-149.
5. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, Buzaid AC, Cochran AJ, Coit DG, Ding S, Eggermont AM, Flaherty KT, Gimotty PA, Kirkwood JM, McMasters KM, Mihm MCJr, Morton DL, Ross MI, Sober AJ, Sondak VK. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 2009; **27(36)**: 6199-206.
6. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Ding S, Byrd DR, Cascinelli N, Cochran AJ, Coit DG, Eggermont AM, Johnson T, Kirkwood JM, Leong SP, McMasters KM, Mihm MCJr, Morton DL, Ross MI, Sondak VK. Multivariate Analysis of Prognostic Factors Among 2,313 Patients With Stage III Melanoma: Comparison of Nodal Micrometastases Versus Macrometastases. *J Clin Oncol* 2010; **28:** 1-9.
7. Seledtsov VI, Felde MA, Samarin DM, Seledtsova GV, Shishkov AA, Niza NA, Turumin JL, Kashchenko EA, Poveshchenko OV, Kozlov VA. Immunological and clinical aspects of xenovaccinotherapy application for the treatment of melanoma. *Russian Oncological Journal* 2006; **4**: 23-28. [Article in Russian]

8. Seledtsov VI, Shishkov AA, Surovtseva MA, Samarin DM, Seledtsova GV, Niza NA, Seledtsov DV. Xenovaccinotherapy for melanoma. *Eur J Dermatol* 2006; **16(6)**: 655-61.

References (Pathogenetic treatment of melanoma with disulfiram):

9. Cen D, Gonzalez RI, Buckmeier JA, Kahlon RS, Tohidian NB, Meyskens FL Jr. Disulfiram induces apoptosis in human melanoma cells: A Redox-related process. *Mol Cancer Ther* 2002, **1:** 197-204.
10. Cen D, Brayton D, Shahandeh B, Meyskens FL Jr, Farmer PJ. Disulfiram facilitates intracellular Cu uptake and induces apoptosis in human melanoma cells. *J Med Chem* 2004; **47(27)**: 6914-6920.
11. Brar SS, Grigg C, Wilson KS, Holder WD Jr, Dreau D, Austin C, Foster M, Ghio AJ, Whorton AR, Stowell GW, Whittall LB, Whittle RR, White DP, Kennedy TP. Disulfiram inhibits activating transcription factor/cyclic AMP-responsive element binding protein and human melanoma growth in a metal-dependent manner in vitro, in mice and in a patient with metastatic disease. *Mol Cancer Ther* 2004; **3(9)**: 1049-1060.
12. Ding W-Q, Liu B, Vaught JL, Yamauchi H, Lind SE. Anticancer Activity of the Antibiotic Clioquinol. *Cancer Res* 2005; **65(8)**: 3389-95.
13. Daniel KG, Chen D, Orlu S, Cui QC, Miller FR, Dou QP. Clioquinol and pyrrolidine dithiocarbamate complex with copper to form proteasome inhibitors and apoptosis inducers in human breast cancer cells. *Breast Cancer Research* 2005, **7(6)**: R897-R908.
14. Chen D, Cui QC, Yang H, Dou QP. Disulfiram, a clinically used anti-alcoholism drug and copper-binding agent, induces apoptotic cell death in breast cancer cultures and xenografts via inhibition of the proteasome activity. *Cancer Res* 2006; **66(21)**: 10425-33.
15. Turumin JL. Clinical cases of pathogenetic treatment of patients with primary and metastatic melanoma with disulfiram (drops, tablets), $CuSO_4$ (drops) and $ZnSO_4$ (zinc ointment, tablets). 2010: 1-7.

Patents (USA) (Pathogenetic treatment of melanoma with disulfiram):

16. Method of treating cancer using dithiocarbamate derivatives: *Patent US 6548540 B2* // Publication Date: **04/15/2003**. – Kennedy TP.
17. Method of treating cancer using tetraethyl thiuram disulfide: *Patent US 6589987 B2* // Publication Date: **07/08/2003**. – Kennedy TP.
18. Method of treating cancer using dithiocarbamate derivatives: *Patent US 6706759 B1* //. Publication Date: **03/16/2004**. – Kennedy TP.
19. Regulation of NAD(P)H oxidase growth and transcription in melanoma cells: *Patent US 6987127 B2* // Publication Date: **01/17/2006**. – Kennedy TP.
20. Method of treating cancer using dithiocarbamate derivatives: *Patent Application 20070232692* // Publication Date: **10/04/2007**. – Kennedy TP.
21. Method of inhibiting ATF/CREB and cancer cell growth and pharmaceutical compositions for same: *Patent US 7816403 B2* // Publication Date: **10/19/2010**. – Kennedy TP.
22. Injectable fomulations of disulfiram for the treatment of alcoholism: *Patent US 4678809* // Publication Date: **07/07/1987**. – Phillips M.
23. Use of disulfiram to prevent cardiovascular damage: *Patent US 5206264* // Publication Date: **04/27/1993**. – Marangos PJ.
24. Method and compositions for inhibiting tumor cell metabolism: *Patent US 5240914* // Publication Date: **08/31/1993**. – Rubin D.
25. Use of dithiocarbamates to treat myelosuppression: *Patent US 5294430* // Publication Date: **03/15/1994**. – Borch RF, Schmalbach TK.
26. Use of disulfiram for neuronal protection: *Patent US 5373021* // Publication Date: **12/13/1994**. – Marangos PJ.
27. Methods for in vivo reduction of nitric oxide levels and compositions useful therefore: *Patent US 5756540* // Publication Date: **05/26/1998**. – Lai Ching-san.
28. Treatment for atherosclerosis and other cardiovascular and inflammatory diseases: *Patent US 5792787* // Publication Date: **08/11/1998**. – Medford RM, Alexander WR, Offermann MK.
29. Pharmaceutical compositions comprising disulfiram: *Patent US 6288110* // Publication Date: **09/11/2001**. – Marikovsky M.
30. Methods for in vivo reduction of free radical levels and compositions useful therefore: *Patent US 6469057 B1* // Publication Date: **10/22/2002**. – Lai Ching-san.
31. Disulfiram doses and treatment regimen suitable for treatment of angiogenesis-dependent disorders: *Patent Application US 20100099757* // Publication Date: **04/22/2010**. – Israeli-Shalev Y, Bar-On A.
32. Implants containing disulfiram and an anti-inflammatory agent: *Patent Application US 20100196436 A1* // Publication Date: **08/05/2010**. – Gooberman L.L.
33. Aldehyde dehydrogenase inhibitors as novel depigmenting agents: *Patent Application US 20100227920* // Publication Date: **09/09/2010**. – Ganesan A, White MA, Farmer PJ.
34. Treatment of melanoma using N,N-dimethylglycine: *Patent 4994492* // Publication Date: **02/19/1991**. – Kendall R.V., Lawson J.W., Reap E.A.
35. Inhibition of melanogenesis and melanoma metastasis with p-aminobenzoic acid (PABA): *Patent US 7691905 B2* // Publication Date: **04/06/2010**. – Brooks PC, Morais D, Rodriguez D.
36. Use of gallium (III) complexes for the treatment of melanomas: *Patent US 7919486 B2* // Publication Date: **04/05/2011**. – Keppler B.
37. Treatment of inflammatory, cancer, and thrombosis disorders: *Patent US 8148416 B2* // Publication Date: **04/03/2012**. - El-naggar MM, Mousa AS.
38. Treatment of melanoma: *Patent US 8163702 B2* // Publication Date: **04/24/2012**. – Tuthill CW, Rudolph AR.