Afterhistory of the oncological patients treatment using amitozyn preparation

V.M. Kovalchuk, B.M. Gulya, N.R. Berdichevska, A.I. Potopalsky

Zhitomir Regional Oncologic Dispensary, Ministry of Health of Ukraine, Zhitomir, Ukraine
Institute of Health Promotion and Rebirth of People of Ukraine, Kyiv, Ukraine

According to the information of the International Union of Fight against Cancer about 80% of the human malignant neoplasms are the long-term results of environmental factors negative influence, individual way of life and also smoking and alcohol abuse.

After Chernobyl disaster the oncopathology incidence of the region's population increased on 10% comparing to a period before the disaster.

Depending on disease localization the maximal growth registered among thyroid gland cancer patients 4.8 times.

Among female population, growth of the breast malignant neoplasms 2.6 times, neck of uterus – 1.3 times and among male population, growth of the prostate malignant tumors 2.4 times, mouth cavity 1.6 and urinary bladder 1.7 times are registered.

Drastic melanoma incidence 9.1% increasing and metastatic neck lesion without initial focus on 25.8% are observed too.

Scientific medicine is not always effective in oncological disease treatment – there are frequent complications after surgical treatment, adverse reaction to chemical preparations, to radiotherapy and to the other treatment methods that does not allow achieving desired results.

All over the world about 1500 new antineoplastic drugs are tested annually, nevertheless, not more then one preparation per year is introduced in the clinical practice (S.A. Shalimov, L.V. Keisevich, I.I. Volchenkova, 1996).

These and other problems constrain to seek out the new more effective low toxic drugs. The Ukrainian scientists have made considerable contribution in tumor

chemotherapy development. We should notice such considerable achievements as elaboration of the original antitumor preparation Amitozyn from a new group of antineoplastic agents – alkyled by thiophosphamide of Chelidonium majus alkaloids. Amitozyn acts as an activating regulator of the immune system and is an effective antitumor preparation. It enhances the immune reactions on malignant cells and has no mutagenic, teratogenic and carcinogenic properties. Thus, the immunomodulatory effect is achieved that brings to the immune status normalization, especially evident in the cases of pathologic changes (A.I. Potopalsky, L.I. Petlichna, S.B. Ivasivka, 1989).

Amitozyn treatment of the oncologic patients has been conducted at Zhitomir regional oncologic dispensary (ZROD) since 1965. The aim of research was studying the short-term and long-term results and also frequency of cancer metastasis relapse during combined Amitozyn treatment depending on the stage of disease, anatomical growth and tumor localization.

Several clinical examples of Amitozyn therapy are given below:

Patient L., 1923 year of birth. Outpatient's card is №2605. On regular medical check-up had been since 10.02.1972 with diagnosis: thyroid gland cancer. $T_3N_xM_0$. 17.02.1972 in the territorial municipal union (TMU) #1 of the city Zhitomir the operation – strumectomy was conducted. Pathohistologic conclusion № 1063 – follicular Ca from 26.02.1972. In the postoperative period from 10.03.1972 - 22.03.1972 X-ray therapy in cumulative dose 5505 was conducted. 13.06.1972 control. Examination of the patient in ZROD. Metastases in the neck lymph nodes were revealed. In the postoperative scar area from the right of supraclavicular area neoplasm of 3 cm in diameter was revealed, it was dense, motionless. Puncture was conducted – cytology – elements of malignant growth. Radiography of the skull was conducted – pathologic changes were not revealed. Patient underwent 2 courses of amitozyn treatment at dose 1 ml i.m. №15 with one month break. 21.01.1975 – control. Observation of the patient. Mts in the right supraclavicular area was not revealed, peripheral lymph nodes were not expanded. Patient underwent radiography of the skull. In the frontal and occipital bones area, distraction niduses with indistinct borders in diameter of 0.4 cm were detected. Conclusion: metastases in the frontal and occipital bones. It was conducted third course of amitozyn treatment at dose 1 ml i.m. №15. 18.09.1975 control radiography of the skull, X-ray photography is the same as previous one from 18.09.1975. From 05.10.1975 patient underwent the fourth course of amitozyn treatment at dose 1 ml i.m. №15. In 1976, patient underwent the fifth course of amitozyn treatment at dose 1 ml i.m. №10. In 1977, 1978, 1979, 1980, patient also underwent the courses of amitozyn treatment at dose 1 ml i.m. №10. 25.07.1983 control X-ray repeated examination was conducted: radiography of the chest organs and the skull. Pathologic changes were not revealed. 30.03.1984 control. Observation. Recurrence and Mts of the affection were not revealed. X-ray repeated examination was conducted. The patient continues amitozyn treatment as prevention 1 time per 2 years at dose 1 ml i.m. №10, phytotherapy. 22.01.2000 control. Examination of the patient in ZROD. Recurrence and Mts were not revealed. The patient continues phytotherapy.

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Patient H., 1925 year of birth. Outpatient's card is № 3048. On dispensary registration in ZROD had been since 1969 with diagnosis: ovarian carcinoma $T_4N_2M_0$. In June 1969 in ROD the operative treatment – palliative amputation of the uterus and its appendages was conducted. At the operation was revealed tumor invasion in the urinary bladder along the posterior wall. Pathohistologic conclusion № 3617 from 03.07.1969: adenocarcinoma. At the postoperative period the patient underwent 4 courses of amitozyn treatment at dose 1 ml i.m. №10 in a day with one month break. At the control observation of the patient, after treatment courses had been conducted, clinical data about resumption of the tumor growth and metastatic affection were not revealed. Annually the patient had dispensary observation at gynecologist in ZROD, and also in the TMU domiciliary. In April 1996, the patient felt pains in the upper part of an abdominal cavity, periodical presence of the dark blood in stool, the patient lost weight, vertigo appeared, bad appetite. In TMU the patient had endoscopic observation: stomach polyp of a large size with destruction and hemorrhage areas. Conservative antianemic therapy was conducted. 26.03.1996 the patient was sent to ROD for further treatment. 03.04.1996 the patient had endoscopic observation: in the stomach body area at the greater curvature was found exophytic tuberous neoplasm up to 8 cm with uneven surface and area of destruction in the centre. Pathohistologic conclusion № 383 - adenocarcinoma. Conclusion: carcinoma of the stomach.

After anteoperational preparation and repeated examination of the patient, 17.04.1996 the operative treatment was done: gastrotomy, polipectomy with stomach wall resection, stomach wall closure. During operative intervention at abdominal cavity inspection, along the urinary bladder posterior wall, scar of 1x7 cm size was revealed. At the area of liver portal were different at size metastatic nodes with invasion in Truncus ciliacus. Postoperative pathohistologic conclusion № 3267-72 from 23.04.1996: adenocarcinoma. At postoperative period complications were not observed. The patient underwent course of amitozyn treatment at dose 1 ml i.v. №10. In a month in TMU the second course of amitozyn treatment at the same dose was conducted. 13.02.1997 at the control observation of the patient in ZROD ultrasound and endoscopic repeated examination was conducted. Recurrence and metastatic affection were not revealed. In 1998-2000 at the control observations of the patient recurrence was not revealed. The patient continues phytotherapy course.

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Patient Yu. 1966 year of birth. Outpatient's card is № 10332. On dispensary registration in ZROD had been since 23.11.1990 with diagnosis: thyroid gland cancer. $T_3N_2M_0$. 23.11.1990 in the Ukrainian Research Institute of Endocrinology (URIE), Kyiv, the operative treatment – total strumectomy was conducted. Pathohistologic conclusion № 857 – follicular papillary cancer. 20.12.1990 the patient was sent to ROD for further treatment. At the patient observation in the postoperative scar area, solid metastatic nodes of 2x1 cm size in diameter were revealed, and in the sinister supraclavicular area – was neoplasm of 6x4 cm size, solid, immovable. At paracentetic cytological examination of the tumor malignant cells were revealed. From 25.12.1990 - 22.01.1991 the patient underwent radiation therapy course at total dose 40 Gy. After radiation therapy the patient felt no improvement. The patient was sent for the repeat operative treatment in the Ukrainian Research Institute of Oncology and Radiology, Kyiv. In March 1991, the operative intervention was conducted – inspection of the tumor, the sinister pectoral lymphatic duct ligation. It was impossible to remove neoplasm in connection with its common carotid artery extension. Postoperative diagnosis: thyroid gland Ca, after combined therapy state. Complications: progressive disease, the sinister supraclavicular area metastasis. Pain syndrome. Intoxication. Clinical group IV. The patient was prescribed symptomatic treatment with narcotic use in TMU domiciliary. From 16.04.1991 the patient underwent the first course of amitozyn treatment at dose 1 ml i.m. №15 in a day. 23.07.1991 – the control observation of the

patient in ZROD. The patient had insignificant pain disturbances in the neoplasm area. The sinister supraclavicular area metastasis decreased. The patient underwent the second course of amitozyn treatment at prescribed above dose. 05.11.1991 the patient was observed by ZROD oncosurgeon. The patient had no particular complains. In the sinister supraclavicular area the tumor was not palpated, evident fibrosis of the soft tissues in this area. The patient underwent the third course of amitozyn treatment at dose 1 ml i.m. №10, in 6 months – the fourth course of treatment at the previous dose of the preparation. After that the patient underwent two more preventive courses of amitozyn treatment. In ZROD 1 time per year ultrasound of the neck was conducted. The pathological changes were not revealed, the local lymphatic nodes were not oversized. 03.08.2000 the control observation of the patient in ZROD. Recurrence and Mts data were not revealed, the head and neck computer tomography was conducted. The patient continues treatment: substitutive hormonotherapy and phytotherapy.

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Patient L. 1948 year of birth. Outpatient's card is № 2946. From 15.06.1992 had been on registration with diagnosis: stomach Ca. $T_3N_2M_0$. 21.06.1992 the operative treatment – gastrectomy was conducted. Pathohistologic conclusion № 7329 – low differentiated carcinoma. In connection with that fact the patient had one kidney, chemotherapy courses were not conducted. The patient underwent 4 courses of amitozyn treatment at dose 1 ml i.v. №10 in a day; the courses were conducted with 6 months break. At the control observations and repeated examinations of the patient, recurrence and Mts data were not revealed.

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Patient K. 1980 year of birth. Outpatient's card is № 2112. From 1996 had been on registration with diagnosis: head skin melanoma recurrence $T_3N_2M_0$. In August 1996 the patient was operated in TMU. From 30.10.1996 - 17.12.1996 combined treatment in ZROD was conducted: fore operative intensive course – radiotherapy (at total dose 20 Gy). 01.11.1996 an operation – neoplasm excision with free-flap surgery was conducted. Pathohistologic conclusion № 10161-64 – melanoma of III-IV Clark's invasion level. At the postoperative period the patient underwent three courses of chemotherapy. 22.09.1997 at the control observation of the patient the multiple dark-brown neoplasms in the skin of neck, chest and head area were revealed. Under i.v. anaesthetic, neoplasm excision was done. Pathohistologic conclusion № 4426-27 – melanosis, melanoma of invasion level I. One course of amitozyn treatment at dose 1 ml №10 was conducted. In a month the refresher course of treatment at the same dose was conducted. 16.04.1999 at the control observation of the patient lower extremity, abdominal wall, back, chest and head skin melanosis was revealed. 19.04.1999 the patient was consulted in the Ukrainian Research Institute of Oncology, Kyiv, by the Doctor of Medical Science I.S. Korovin. It was recommended to fulfill palliative course of the close-focus roentgen therapy + locally chemotherapy methotrexate at dose 5 mg, 100 mg per one course, immunotherapy course with laferon 30 mln. The patient underwent treatment course: on the focuses – total dose 10956, methotrexate 100 mg, laferon 30 mln. 08.10.1999 the control observation of the patient in ZROD. Lower extremity, abdominal wall, back, chest and head skin melanosis of 0.3 – 0.4 cm size was revealed. The patient underwent III course of amitozyn treatment. In a month IV course of amitozyn treatment №10 at dose 1 ml i.v. was conducted. 20.03.2000 the control observation of the patient – focal melanosis and metastasis data were not revealed. The patient continues amitozyn treatment and phytotherapy.

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Patient K. 1937 year of birth. Outpatient's card is № 9900111. On dispensary registration had been since 16.04.1998 with diagnosis: left shoulder skin melanoma recurrence. Clinical group II. In TMU №1 from 01.03.1998. The operation – removal of the left shoulder neoplasm under local anesthesia, was conducted. Pathohistologic conclusion: melanoma of III-IV Clark's invasion level from 09.03.1998. From 16.04.1998 in ZROD, the combined treatment was conducted: the operative treatment – removal of the postoperative scar widely within the boarders of the unaffected tissues. At the postoperative period the course of amitozyn treatment №10 at dose 1 ml i.v. was conducted. In connection with Mts – affection of the left forearm skin the second course of amitozyn treatment at previous dose was conducted, Mts at the control observation was not revealed. From 16.10.1998 - 30.10.1998 the 3rd course of amitozyn treatment №10 at dose 1 ml i.v. was conducted. The patient annually undergoes the control observation in ZROD. After-observation. Recurrence and Mts data were not revealed. The patient continues phytotherapy.

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Patient P. 1933 year of birth. Outpatient's card is № 1134. On dispensary registration had been since 24.12.1998 with diagnosis: recurrence of the under lip Ca, clinical group II. In Drogobich city in 1998 the close-focus roentgenotherapy at total dose 7684 was conducted. 24.12.1998 the patient appealed to ZROD in connection with disease progressing: in the under lip area, angle of mouth – neoplasm with unpleasant smell, immovable, in the submaxillary area Mts node for 3 cm size, immovable. The puncture biopsy was conducted. Cytology № 10832 from 24.12.1998 – cornu epidermoid cancer. The patient underwent combined treatment: the radiotherapy course with total dose 40 Gy together with cancer invasive introduction of amitozyn preparation № 15 at dose 1.5 ml. After treatment conduction – recurrence of neoplasm and Mts node – was 50 %. The operative treatment was conducted. Brunse's resection of the under lip with cheiloplasty, Vanach's operation. Pathohistologic conclusion: № 363 – 66 radiation pathomorphism of the cornu epidermoid cancer from 26.01.1999. The control observation of the patient 31.07.2000: recurrence and Mts affection clinical data were not revealed. The patient continues amitozyn treatment, phytotherapy.

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Patient P. 1954 year of birth. Outpatient's card is № 2650. On dispensary registration had been since 17.03.2000 with diagnosis: nasopharynx Ca group III, clinical group II. $T_3N_1M_1$ complication: neck metastases from the left, metastatic pleurisy from the left. Intoxication. Diagnosis: verified cytological № 2895. Low differentiated nasopharynx carcinoma from 21.03.2000; № 3865. 69-71 cell complexes of the low differentiated adenocarcinoma (from the pleural cavity) from 17.04.2000; № 1103 – neck adenocarcinoma metastases from 21.03.2000. The patient was repeatedly observed in corpore: the ENT-doctor observation, radiography, bronchoscopy, esophagogastroscopy, magnetic resonance tomography – conclusion: left-side metastatic pleurisy, lymph nodes affection from the left, nasopharynx cancer. From 21.03.2000 the patient underwent combined treatment: radiotherapy course on the primary focus and neck Mts at total dose 60 Gy with 3 weeks break and course of amitozyn treatment pleural intake at dose 1 ml in a day №10 and №5 at dose 1 ml i.v. 25.07.2000 the control observation of the patient in ZROD, metastatic pleurisy data were not revealed. Neck Mts nodes were not palpated, locally the nasopharynx neoplasm resolved. At defined time the patient had amitozyn treatment.

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Patient S. 1930 year of birth. Outpatient's card is № 4811. On dispensary registration had been since 01.06.2000 with diagnosis: the under lip Ca group III clinical group II. $T_3N_0M_0$. Cytology № 5867 epidermoid low differentiated cancer. From 01.06.2000 combined treatment was conducted: radiotherapy course at total dose 40 Gy together with course of amitozyn treatment (regionally – intra-arterial injection) № 10 at dose 1ml. 25.07.2004 the control observation of the patient, the affection of an under lip data clinically and cytologically were not revealed. The patient continues phytotherapy.

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Patient T. 1940 year of birth. Outpatient's card is № 1347. On dispensary registration had been since 17.08.1995 with diagnosis: lower third part of the right lower leg skin melanoma T_3NxMo. 18.08.1995 the operative treatment was conducted – neoplasm removal with free-flap surgery of the wound. Pathohistologic conclusion: № 25624 – melanoma of III Clark's invasion level. 19.02.1997 the control observation of the patient: multiple skin and lymph nodes of the right lower extremity metastases were revealed. The first course of amitozyn treatment №15 at dose 1 ml i.v. in a day was conducted. At the control observation of the patient in a month, the metastasis regression on 50% was revealed. The patient underwent II course of amitozyn treatment at previous preparation dose. In a month patient underwent III course of amitozyn treatment at previous preparation dose. 03.08.1998 in the lower leg and thigh area three metastatic nodes of 1 cm size in diameter had left, others had resolved. 22.08.1998 cryodestruction with metastases removal was conducted. The patient underwent IV course of amitozyn treatment №10 i.v. The patient continues treatment – phytotherapy. At defined time the patient had no disease recurrence.

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Patient G. 1955 year of birth. Outpatient's card is № 7862. On dispensary registration had been since 05.10.1995 with diagnosis: neck metastasis without primary focus T_0N_2Mo. 04.10.1995 puncture biopsy of the neoplasm – cytology – adenocarcinoma metastasis. The combined treatment was conducted: preoperative course of PT at total dose 40 Gy. 17.10.1995 operation – neoplasm removal. Pathohistologic conclusion: № 9019-29 – follicular Ca from 23.10.1995. 29.02.1996 control observation by oncosurgeon –metastasis of the right neck area was revealed. Preoperative course of PT at total dose 40 Gy was conducted. 10.12.1996 operation – from the right Krail's operation. Pathohistologic conclusion: № 11426-33 – lymph nodes metastases of follicular Ca from 16.12.1996. At the control observation of the patient in 3 months metastatic affection of the neck lymph nodes from the left was revealed and proved cytologicaly. Three courses of amitozyn treatment with one month break №10 at dose 1 ml in a day were conducted. At the control observation after the third course of treatment, metastases in the neck area were not revealed. The patient was repeatedly observed: ultrasound diagnostics, computer tomography. 28.01.2000 the control observation of the patient, recurrence and metastases data were not revealed.

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Patient K. Outpatient's card is № 13526. On dispensary registration in ZROD had been since 2000 year with diagnosis: angiofibrosarcoma of the left temporal region, clinical group II. In 2000, palliative operation was conducted – neoplasm removal with postoperative course of radiotherapy at total dose 40 Gy. In 2003, the patient was sent to ZROD after the patient had been consulted in the Ukrainian Research Institute of Oncology and Radiology, Kyiv. The patient underwent 3 courses of chemotherapy (regionally) in connection with affection of the temporal bone of 6 cm size (computer tomography data). After treatment – the neoplasm regression on 20% was observed. After that, two courses of amitozyn treatment at dose 250 mg per one course were conducted. 2004 – the

control observation of the patient, recurrence data were not revealed, control computer tomography of the head – defect of the temporal bone for about 3 cm size. The patient continues treatment.

At amitozyn use in the treatment of disseminated malignant head and neck tumors, metastatic affection of the neck without primary focus (60 patients had been treated) the complications were not observed.

Two-years survival index, after combined treatment conduction: radiotherapy + poly chemotherapy (the first group of the patients) was (52,2 ± 4,2)%, three-years index – (47±5)%, five-years – (40,2 ± 5,2)%. Before one year – 8 (25%) patients died. Recurrence, cancer metastases were revealed at 7 (22%) patients, among them at the period from 6 months up to 2 years. Two-years survival index, after combined treatment conduction: radiotherapy + Amitozyn (the second group) was (82,2 ± 4,4)%, three-years index – (70,1±5)%, five-years – (50,3 ± 5,4)%. Before one year – 4 (13,3%) patients died. Recurrence, cancer metastases were revealed at 5 (8,1%) patients, among them at the period from 8 months up to 2 years.

Conclusions

1. Wide use of amitozyn in present-day oncological patients' treatment will give an opportunity to improve long-term results of all age groups patients' survival.
2. Use of the preparation in combined treatment prevents from negative complications appearance. For detailed study of antineoplastic agents and their derivatives, it is necessary to continue researches. The long-term results prove the preparation use expediency in the present-day oncological patients' treatment.

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