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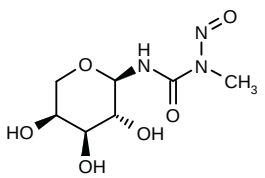
CCC: 0377-8282/2003

Aranoza+

Treatment of Melanoma
Nitrosourea

CRC-0510375

3-(α-L-Arabinopyranosyl)-1-methyl-1-nitrosourea



$C_7H_{13}N_3O_6$
Mol wt: 235.198
CAS: 167396-23-8
EN: 191979

Abstract

Aranoza is a 1-methyl-1-nitrosourea derivative with potent antitumor activity. Aranoza was shown to have inhibitory effects on DNA, protein and RNA synthesis in i.p. implanted L1210 leukemia cells in mice and was a powerful inducer of single-strand breaks in DNA of L1210 cells. It strongly inhibited the activity of DNA polymerase-α and induced the formation of a large number of O^6-methylguanine (O^6-MG) adducts in L1210 leukemia cells which persisted in cellular DNA over extended periods of time. The mechanism of cell resistance to aranoza involves, among other factors, an increase in O^6-MG transferase activity which diminishes the cytotoxic effect of the drug. In clinical trials, uterine sarcoma, breast carcinoma, nasopharynx cancer, Hodgkin's, and non-Hodgkin's lymphomas showed some response to aranoza treatment. The best results, however, were seen in malignant melanoma. Side effects of the drug were acceptable, and after its activity was confirmed by several clinical trials in melanoma patients it was approved for clinical use in patients with disseminated malignant skin melanoma. Further clinical trials are in progress to evaluate new aranoza-containing combinations in patients with melanoma and small cell lung carcinoma.

+See previous monograph published in Drugs of the Future 1994, 19(5): 439.

Synthesis

The synthesis of aranoza (IV) was accomplished by the condensation of *N*-methylurea (II) with L-arabinose (I), which yields 3-α-L-arabinopyranosyl-1-methylurea (III), followed by nitrosation of the latter (Scheme 1). In slightly alkaline conditions or upon heating, aranoza undergoes intramolecular carbamoylation to produce N^1O^3-carbonyl-α-L-arabinopyranosylamine (V), gaseous N_2 and methanol. It is important that diazomethane (CH_2N_2) is not formed under these conditions as demonstrated by gas chromatography and mass spectrometry (1).

Introduction

N-Alkyl-*N*-nitrosoureas (ANUs) are important antitumor drugs used for the treatment of various malignant neoplasms. Various ANUs, such as 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), 1-(4-amino-2-methyl-5-pyrimidinyl-3-(2-chloroethyl)-3-nitrosourea (ACNU), chlorozotocin and streptozotocin have been widely used in combination chemotherapy of solid tumors (disseminated melanoma, small cell lung carcinoma, brain tumors) and lymphomas. ANUs show no cross-resistance with typical alkylating agents and there are significant differences in the mechanism of action between various drugs belonging to this group.

Under physiological conditions, ANUs decompose spontaneously to yield an alkyldiazohydroxide and the methyl or chloroethyl carbonium ion which alkylate the nucleophilic centers of biomacromolecules, while iso-

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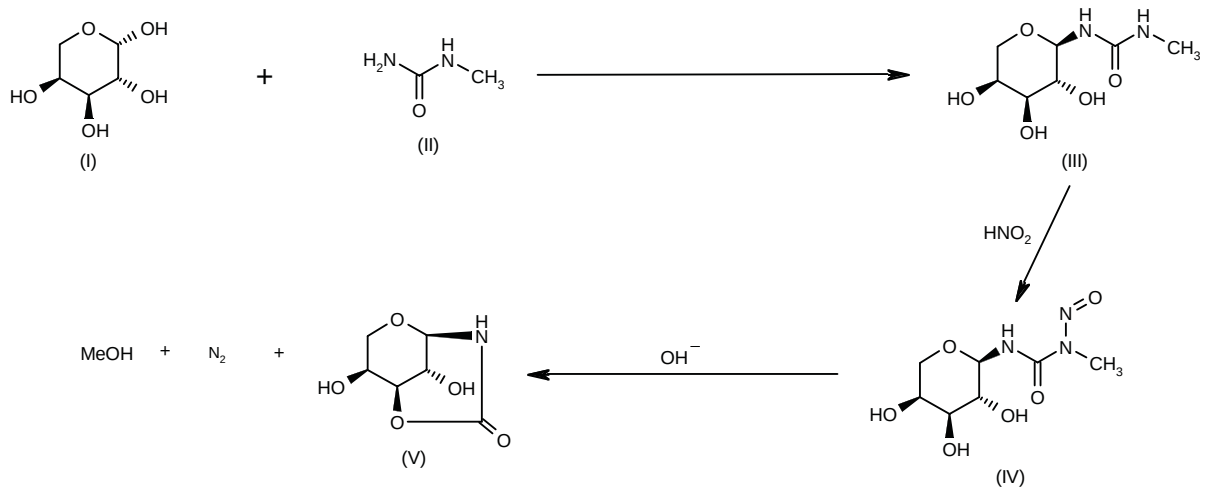
Scheme 1: Synthesis of Aranoza



cyanates carbamoylate intracellular proteins and lipids (2, 3). The antitumor activity of ANUs mainly depends on their alkylating properties; the role of carbamoylation is not exactly clear, but may be related to ANU toxicity.

There is ample experimental evidence indicating that formation and persistence of O^6-alkylguanine (O^6-AG) is important for cytotoxicity of ANUs. O^6-AG adducts in DNA are repaired by O^6-alkylguanine DNA alkyltransferase (O^6-AGT). During the repair of alkylated DNA, O^6-AGT transfers the alkyl group from O^6-AG position to the cysteine moiety in the active site of the enzyme. Cells deficient in O^6-AGT exhibit increased sensitivity to ANUs (Mer^-), while cells with high level of O^6-AGT are resistant to the drugs (Mer^+). O^6-AGT activity in tumor cells may be used for prediction of their sensitivity to ANUs (4). Transfection of Mer^- tumor cells with the O^6-AGT-gene results in the essential increased activity of O^6-AGT and resistance to ANUs (5). Resistance to ANUs, both intrinsic and acquired, is an important issue in cancer chemotherapy. There is only partial cross-resistance between various ANUs (6).

Aranoza (3-α-L-arabinopyranosyl-1-methyl-1-nitrosourea) is an alkylnitrosourea conjugated with a monosaccharide. But in contrast to other carbohydrate-substituted alkylureas such as chlorozotocin and streptozotocin, the structure of the arabinose moiety in aranoza is responsible for very efficient intramolecular trapping of the carbamoyl (–N=C=O) group formed in the process of degradation of the methylnitrosourea moiety under physiological conditions. This is due to the structure of arabinopyranose, which in the process of methylurea destruction easily changes conformation from $^4C_1$ to $^1C_4$ and forms a very stable 2-oxazinone derivative conjugated with the L-arabinose backbone. The trapping of alkylisocyanate produced in the course of aranoza degradation depends on some fortunate configurational and conformational factors.

Pharmacological Actions

The antitumor activity of aranoza was evaluated against a wide spectrum of experimental animal tumors, including leukemias L1210 and P388, plasmacytoma MOPS 406, Lewis lung carcinoma, melanoma B16, sarcomas 37 and 180. The LD_{50} for aranoza is 1150 mg/kg and the LD_{10} is 630 mg/kg. The therapeutic efficacy of aranoza was similar after intravenous, intraperitoneal or subcutaneous single-dose or multiple dose administration to tumor-bearing mice. Aranoza differs from other ANUs by the wide range of doses at which it is therapeutically active: daily doses of 200 and 100 mg/kg administered for 5 days have a similar effect on increasing the life span of tumor-bearing mice (167% and 155%, respectively). Aranoza is 2-fold more effective than 1-methyl-1-nitrosourea (MNU) and streptozotocin, but less active than BCNU and ACNU against L1210 and P388 leukemias. Aranoza was shown to be particularly active against melanoma B16, Lewis lung carcinoma and plasmacytoma MOPS 406. In contrast to streptozotocin, aranoza is not diabetogenic for mice. In experiments with dogs, aranoza did not affect heart, liver or kidney function and did not change the activity of microsomal enzymes (7).

The effects of aranoza were compared with those of MNU on DNA, RNA and protein synthesis, formation of single-strand breaks (SSB), formation of O^6-methylguanine adducts (O^6-MG) in DNA, the activity of DNA polymerases α and β and of O^6-MG DNA-methyltransferase (MGT) using L1210 leukemia cells and L1210/A leukemia cells with acquired resistance to aranoza. L1210/A

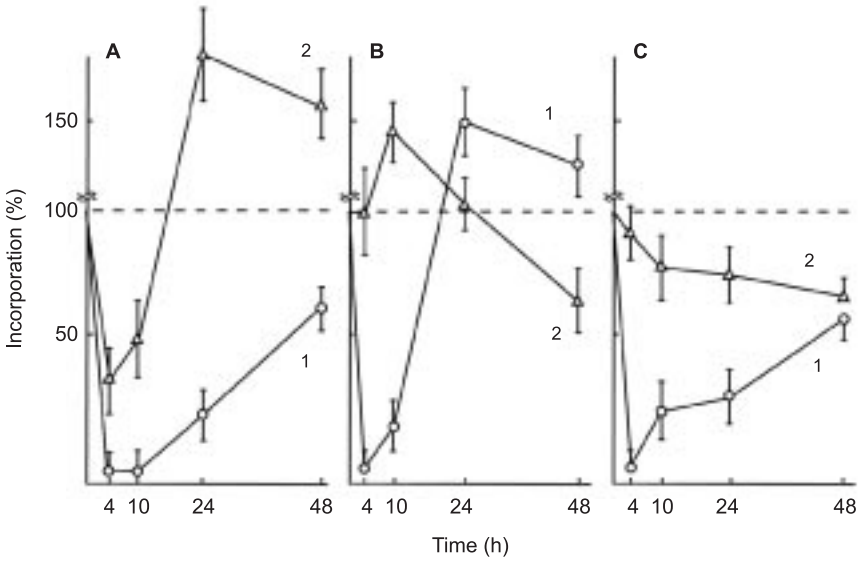


Fig. 1. The effect of aranoza (1) and MNU (2) on the incorporation of 2-^{14}C-thymidine into DNA (a), 2-^{14}C uridine into RNA (b) and L-U-^{14}C lysine into proteins (c) of i.p. implanted L1210 leukemia cells in mice.

leukemia cells are 8.5 times more resistant to aranoza and MNU than L1210 cells. In these experiments, mice were injected with 100,000 L1210 or L1210/A leukemia cells and then aranoza and MNU were administered 120 h later to tumor-bearing mice at single doses of 400 mg/kg and 80 mg/kg, respectively. The details of experimental protocols including analysis of damage in nucleoid structure induced by aranoza and MNU, determination of activities of DNA polymerases α and β were reported earlier (8, 9). The level of MGT activity of extracts of L1210 and L1210/A leukemia cells before drug treatment and at 2, 4, 24, 48 and 72 h after drug treatment *in vivo* was measured by the rapid procedure involving O^6-MG containing oligodeoxynucleotides, followed by immunoprecipitation with highly specific antibody (10). DNA was isolated from L1210 and L1210/A cells before aranoza or MNU injection, and then at 2, 4 and 24 h after drug injection to tumor-bearing mice (11). Determination of O^6-MG adducts in DNA was performed by HPLC and radioimmunoassay using tritiated O^6-MG (12, 13).

The effects of a single injection of aranoza or MNU on the incorporation of radioactive precursors into macromolecules of L1210 leukemia cells growing in mice are shown in Figure 1. Aranoza induced a more marked inhibition of DNA synthesis during 48 h after administration as compared to MNU. The greatest difference between aranoza and MNU was observed for the effect on RNA synthesis. Aranoza induced potent inhibition of RNA synthesis 4-10 h after administration, whereas MNU inhibited RNA synthesis to about 40% of the control level 48 h after its administration. The inhibitory effect of aranoza on protein synthesis was greater than that of MNU.

The level of SSB in DNA induced by aranoza in L1210 cells was maximal 1 h after its administration to tumor-bearing mice. SSB were repaired almost completely within 48 h after araanoza administration. (Fig. 2).

The inhibition of DNA synthesis by aranoza or MNU may be due, in part, to their effect on DNA polymerases. DNA polymerase alpha is the major DNA polymerase of animal cells and is associated mainly with DNA replication, whereas DNA polymerase β plays an important role in the repair of DNA damage induced by various agents (14). We have demonstrated differences in the effects of aranoza on the activity of DNA polymerase α and β. As early as 1 h after administration of aranoza to mice, DNA polymerase α activity in L1210 leukemia cells was reduced by 50% while that of DNA polymerase β showed only a minor change (Fig. 3).

Repaired O^6-MG occurs via MGT reaction and depends on the level of the enzyme. We compared the formation of O^6-MG adducts in DNA and MGT activity in L1210 and L1210/A leukemia cells after treatment with aranoza and MNU. The activity of MGT in lysates of L1210/A cells was about 9 times higher than in L1210 lysates (760 and 83 fmol/mg protein, respectively). The activity of MGT in L1210/A cells was greatly reduced 2 h after administration of a single dose of MNU or aranoza. The activity of MGT showed complete recovery by 48 h and 72 h after MNU and aranoza treatment, respectivel (Fig.4). The recovery was probably due to the synthesis of the new enzyme molecules. The administration of MNU or aranoza to mice bearing L1210 leukemia cells led to a 2-fold decrease in AGT activity, which persisted over 72 h (Fig.5).

Quantitative estimation of O^6-MG adducts in DNA isolated from L1210 and L1210/A leukemia cells in tumor-

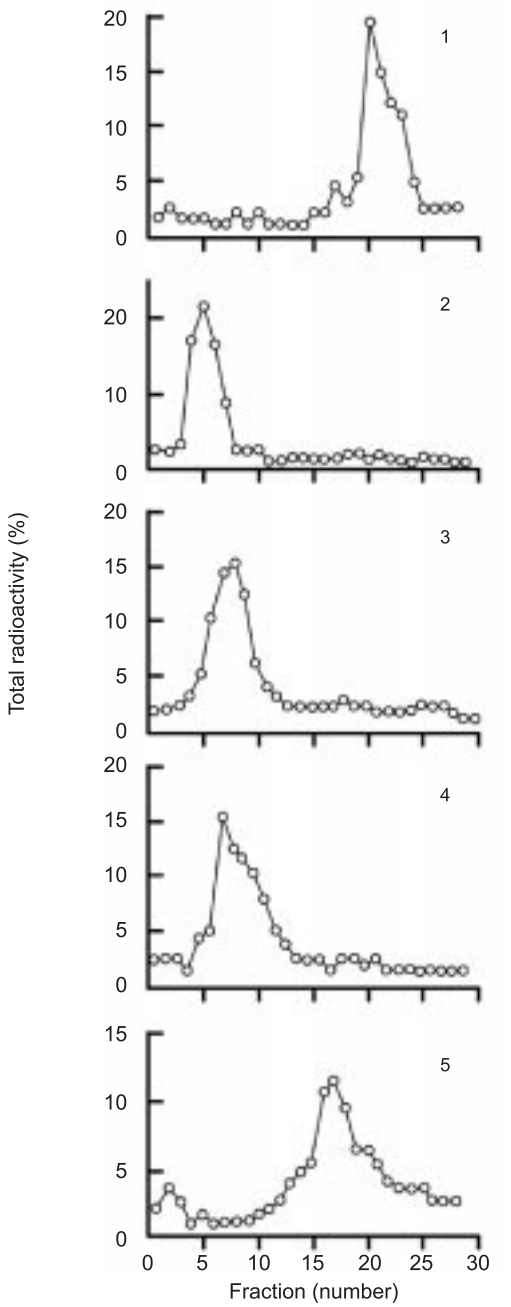


Fig. 2. Sedimentation of L1210 cells nucleoids in neutral sucrose gradients at various times after treatment of cells *in vivo* with aranoza.

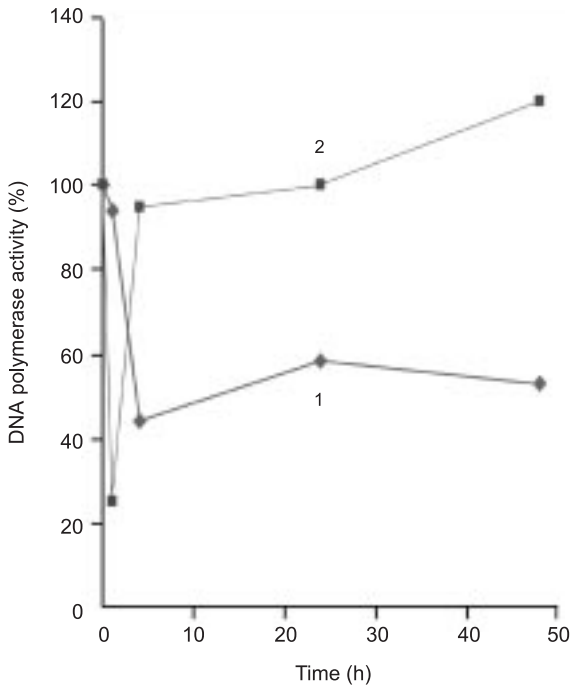


Fig. 3. The effect of aranoza on DNA polymerase α (1) and β (2) activities in L1210 leukemia cells *in vivo*.

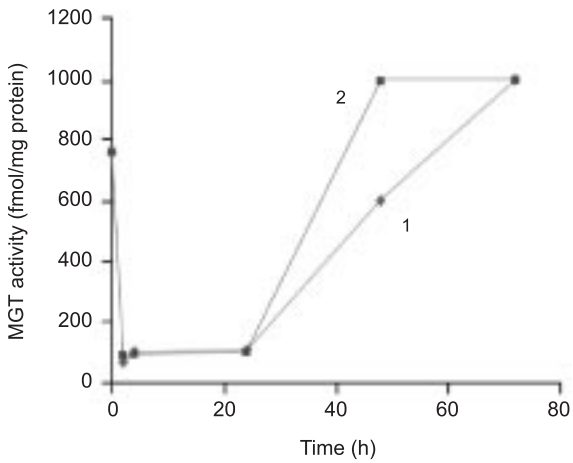


Fig. 4. The effect of aranoza (1) and MNU (2) on MGT activity in L1210/A leukemia cells. Mean values from 5 mice are presented.

bearing mice after treatment with aranoza or MNU has demonstrated a difference between the drugs and the two strains. Aranoza induced more O^6-MG adducts than MNU, which may have been due to the difference in the therapeutic doses of the drugs (400 and 80 mg/kg, respectively). The depletion of MGT pools in the resistant cells resulted in a decrease in the levels of O^6-MG adducts in DNA. At 2 h after administration of MNU or aranoza to mice bearing L1210/A cells, the levels of O^6-MG adducts in DNA were 30 and 40 μmol/mol G, while in DNA of L1210 cells these values were 190 and 290 μmol/mol G, respectively.

The initially high level of MGT activity in L1210/A resistant cells was responsible for the efficient repair of methylated DNA, and consequently lower cytotoxic activity of both aranoza and MNU. The level of MGT activity in sensitive L1210 cells was not sufficient for the repair of a significant amount of O^6-MG induced by the drugs. It is

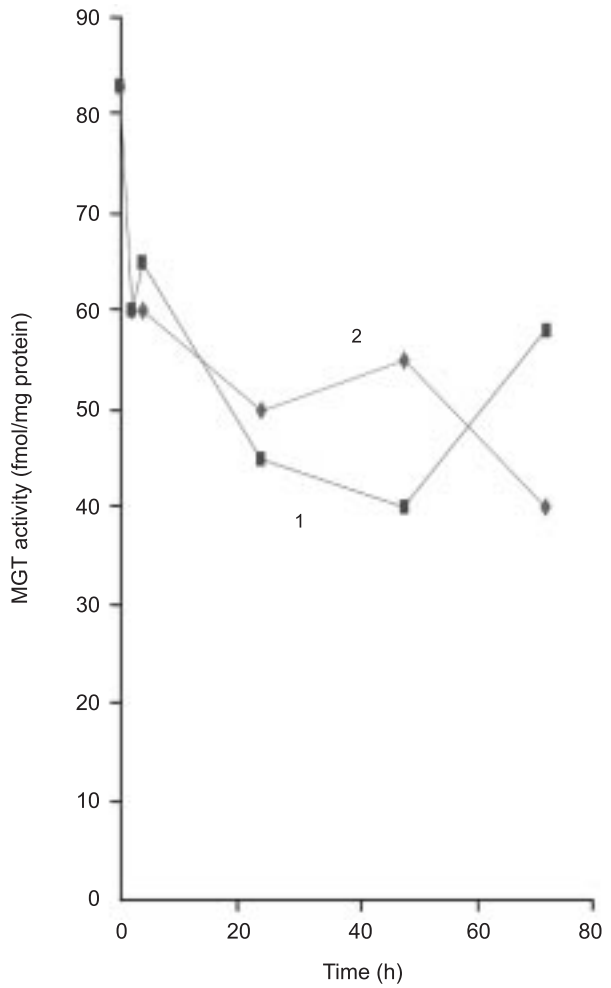


Fig. 5. The effect of aranoza (1) and MNU (2) on MGT activity in L1210 leukemia cells. Data are averages from 5 mice.

likely that the mechanism of resistance to aranoza is associated with high MGT activity in resistant cells.

Metabolism

In vitro alkylating activities of aranoza and MNU are similar. However, the carbamoylating activity of aranoza is 2.5 -fold lower than that of MNU. This once again confirms the absence of correlation between carbamoylating and antitumor activity of ANUs (15). The low carbamoylating activity is in agreement with the easy intramolecular carbamoylation and the formation of (V), as shown in Scheme 1.

Like other ANUs, aranoza rapidly disappears from blood after an i.v. injection. Ten minutes after a single injection of aranoza to rats, only 4% of the drug could be determined by HPLC, and the half-life was about 15 min.

N_1O_3-carbonyl-α-L-arabinopyranosylamine, a metabolite of aranoza, was identified by HPLC method in blood serum of patients after i.v. administration of aranoza (16).

Clinical Studies

Phase I clinical trials with aranoza were carried out in patients with different histologically confirmed malignant tumors using WHO criteria for the evaluation of response and assessment of toxicity. Aranoza was supplied in 50 ml glass vials containing 500 mg of aranoza and polyvinylpyrolidone. The drug was diluted in a 5% glucose solution immediately before use and administered by i.v. bolus injection. The starting daily dose for phase I clinical trials calculated on the basis of the lowest toxic dose (LTD) in dogs was 44 mg/m^2, which was administered i.v. for 3 consecutive days. Doses were increased using the modified Fibonacci scale and toxic reactions were recorded at each dose level.

Reversible myelosuppression was the dose-limiting toxicity observed in 55.3% of patients (grade 3-4 in 33%) at daily doses above 792 mg/m^2. Under these conditions, 2 patients had thrombocytopenia (platelet counts 300,000 and 700,000). The most common side effects were nausea and vomiting, occurring in 71.8% of patients. Transient diarrhea was reported in 10.2% of patients. Mild reversible renal toxicity (increase of BUN, creatinine levels > 1.25 mg/dl and proteinuria) was observed in 7% of patients. Fever, dermatitis and phlebitis occurred in a few patients receiving aranoza at doses above 528 mg/m^2 x 3 (Table I). As a result of this trial, a daily dose of 550-800 mg/m^2 i.v. given 3 times (daily or every other day) every 4 weeks was selected for the phase II trial. Marked responses to aranoza in melanoma patients were registered during the trial and included 1 complete response (CR) and 2 partial responses (PR) in 23 of the evaluable patients, resulting in an overall response rate (RR) of 13%.

In a multicenter phase II clinical trial, 337 cancer patients were treated with aranoza as described above. The results of this phase II trial confirmed the antitumor activity of aranoza in malignant melanoma (CR: 3.9%, PR: 20.9%, RR: 24.8%). Furthermore, potent antitumor activity was reported in patients with uterine sarcoma. Of 5 patients with leiomyosarcomas, 2 had complete response and 2 had partial response. Complete response was observed in 1 patient each with carcinosarcoma and stromal uterine sarcoma. Remissions lasted between 5 and 16 months. There were also responses in patients with head and neck tumors; 1 patient with nasopharynx cancer had complete remission which lasted for 18 months and 1 patient with oropharynx cancer had partial remission lasting for 4.5 months. In 2 patients with cancer of the thyroid gland, partial remissions lasted 3.5 and 16 months, respectively, and in 1 patient with cylindroma of the maxillary sinus who received 9 courses of aranoza and showed partial response, the time to progression was

Table I: Toxicity of aranoza at different dose levels.

Daily dose mg/m²	Total dose	No. of pts.	Nausea and vomiting				Myelosuppression														
							Leukopenia					Thrombocytopenia									
			1	2	3	Total	1	2	3	4	Total	1	2	3	4	Total	Renal toxicity[1]	Hepato-toxicity[2]	Diarrhea	Fever	Phlebitis
44-145	220-435	20	2	4	1	7 (33%)	1	-	-	-	1	1	-	-	-	-	3	1	-	-	-
220-307	660-921	12	3	3	2	8 (66.6%)	1	-	-	-	1	1	-	-	-	-			2	2	
308-527	924-1581	12	2	7	-	9 (75%)	1	-	-	-	1	-					1	-	1	-	-
528-791	1584-2373	18	1	14	3	18 (100%)	-	-	-	-	-	-	-	-	-	-	1		2	2	-
≥792	>2376	9	1	4	4	9 (100%)	-	2	1	2	5 (55.5%)	-	1	1	-	2 (22.2%)	-	-	4	1	1
Total		71	9	32	10	51 (71.8%)	3	2	1	2	8 (11.2%)	-	1	1	-	2 (2.8%)	5 (7%)	1	9 (10.2%)	5 (7%)	

[1]Increase in BUN and creatinine >1.25 mg/dl. [2]Increase in SGOT/SGPT > 1.25

Table II: Results of a multicenter phase II trial of aranoza treatment in different tumor types.

Tumor	No. of patients	CR	PR	RR, %
Melanoma	129	5 (3.9%)	27 (20.9%)	24.8%
Lung cancer (NSCLC)	53	-	-	-
Gastric carcinoma	29	-	-	-
Colon carcinoma	13	-	-	-
Pancreatic cancer	2	-	-	-
Renal cancer	10	-	1	-
Uterine sarcoma	9	4 (44.4%)	2 (22.2%)	66.6%
Breast cancer	12	2	4	50%
Ovarian carcinoma	6	-	3	-
Bladder carcinoma	1	-	-	-
Testicular cancer	2	-	-	-
Head and neck cancer	25	1 (4%)	5 (20%)	24%
Prostate cancer	5	-	-	-
Hodgkin's disease	11	-	4 (36.4%)	36.4%
Lymphosarcoma	20	1 (5%)	7 (35%)	40%
Other	12	-	-	-
Total patients	337	-	-	-

8 months. Of 12 patients with breast cancer, 2 entered complete remission lasting 7 and 8 months, respectively, and 4 had partial remissions lasting 2-7 months. Of 11 previously treated patients with Hodgkin's disease, 4 (36%) showed a partial response lasting for 2-2.5 months. Of 20 patients with lymphosarcoma, 1 had a complete response and 7 a partial response, for an overall response rate of 40% (Table II).

This trial also confirmed that aranoza was relatively well tolerated. All side effects were reversible. The most common were nausea and vomiting in 73.9% of patients, although only 4 patients (1.2%) discontinued treatment. There were no drug-related deaths. Aranoza caused dose-dependent myelosuppression, with grade 3-4 leukopenia developing in 10% of patients and grade 1-2 thrombocytopenia in 3.3 % of patients between days 14 and 28 of treatment (17).

A disease-oriented phase II trial of aranoza was conducted in 48 patients with disseminated skin melanoma. All patients received 750-800 mg/m² of aranoza i.v. daily on days 1-3 every 4 weeks. Restaging was performed after every 2 treatment courses. Treatment response was observed in 11 of the 48 patients (RR: 23%). Complete and partial responses were seen in 6 (12.5%) and 5 patients (10.3%), respectively, and 5 patients with minor response were included in the no-change group. Complete responses lasted for 6-18 months (average 11 months). In partial responders, the duration was 14 months. Toxicity was mild and reversible (17).

In another phase II trial, 33 patients with disseminated skin melanoma received aranoza at a dose of 670 mg/m² i.v. on days 1-3 every 4 weeks. A response rate of 18.2% was recorded, although there were no complete responses (18).

In another study in 29 melanoma patients, aranoza was administered at a dose of 830 mg/m² i.v. on days 1, 3, and 5, with treatment being repeated every 4 weeks. The treatment resulted in 2 (6.8%) complete responses

Table III: Results of a randomized trial of aranoza vs. DTIC in patients with disseminated skin melanoma.

Regimen	No. of pts.	CR	PR	RR	Remission (median)	Toxicity Leukopenia Grade 1-2	Nausea/vomiting
Aranoza 670 mg/m^2 i.v. days 1-3 every 4 weeks	114	3.5%	11.4%	14.9%	3.5 mo	21%	66%
DTIC 250 mg/m^2 i.v. days 1-5 every 4 weeks	99	2%	8%	10%	3 mo	24.2%	65.7%

Table IV: Cumulative data on aranoza as monotherapy in disseminated skin melanoma.

Regimen	No. of pts.	CR	PR	RR, %	Ref.
Aranoza 750-800 mg/m^2 i.v. d 1-3 every 4 weeks	48	6 (12.5%)	5 (10.5%)	23	17
Aranoza 750-800 mg/m^2 i.v. d 1-3 every 4 weeks	129	5 (3.9%)	27 (20.9%)	24.8	
Aranoza 830 mg/m^2 i.v. d 1, 3, 5 every 4 weeks	29	2 (6.8%)	3 (10.3%)	17.1	19
Aranoza 670 mg/m^2 i.v. d 1-3 every 4 weeks	33	-	6 (18.2%)	18.3	18
Aranoza 670 mg/m^2 i.v. d 1-3 every 4 weeks	114	4 (3.5%)	13 (11.4%)	14.9	20
Total	353	17 (4.8%)	54 (15.3%)	20.1	

and 3 (10.3%) partial responses, for an overall response rate of 17.1% (19).

A clinical study comparing aranoza with DTIC in patients with histologically confirmed disseminated skin melanoma randomized 215 patients to receive either aranoza 670 mg/m^2 i.v. on days 1, 2 and 3 every 4 weeks or DTIC 250 mg/m^2 on days 1-5 every 4 weeks. Results were evaluated according to WHO criteria after two cycles of chemotherapy, and responders and patients with stable disease were treated up to progression. There was no significant difference in the results between the two arms. The overall RR in the aranoza arm was 14.9% (CR: 3.5%, PR: 11.5%). The overall RR for patients treated with DTIC was 10% (CR: 2%, PR: 8%). In the aranoza group, remissions lasted 1-10 months (median 3.5 months) and in the DTIC group the average duration was 8 months (median 3 months). Toxicity with both regimens was acceptable; 66.6% and 68.7% of aranoza- and DTIC-treated patients, respectively, experienced grade 1-2 nausea and vomiting. Grade 1 leukopenia was observed in 21% and 24.4% of patients in the aranoza and DTIC treatment groups, respectively (Table III) (20).

Analysis of the cumulative data of 5 trials including 353 patients with disseminated skin melanoma and treated with aranoza as a single drug is presented in Table IV. Treatment with aranoza resulted in an overall RR of 20.1% (14.9-24.8%) with complete remissions lasting 6-8 months in 5.3% of patients. The best responses were seen in patients with lymph node, skin and soft tissue metastases. Responses were rare in patients with lung and liver metastases, and no response was seen in patients with bone metastases.

Several clinical studies have evaluated aranoza in combination with interferons or cytostatics. In one study, 70 patients with disseminated skin melanoma were treated with aranoza administered as monotherapy (29 patients) or in combination with interferon alfa-2a (41 patients). In this nonrandomized trial, aranoza was administered at a dose of 830 mg/m^2 i.v. on days 1, 3 and 5 every 4 weeks. A total of 41 patients received additional treatment with interferon alfa-2a, which was started 7-14 days after chemotherapy. The starting dose of interferon was 2x106 IU i.m., 3 times weekly; every week the dose was increased by 2x106 IU up to a daily dose of 10-12x106IU, which was followed by a similarly scheduled deescalation. In responders and patients with stable disease, treatment with interferon (2x106 IU, 3 times a week) was continued up to progression. In the group receiving aranoza in combination with interferon, the response rate was 31.7% (CR: 12.2%), with responses lasting from 3.5 to 30+ months. Among 29 patients treated with aranoza monotherapy, the response rate was 17.1% with a complete response in 2 patients (6.8%) lasting 3 and 6 months, respectively (19).

A randomized study evaluated interferon alpha-n together with aranoza/cisplatin combination in 28 patients with disseminated skin melanoma. Patients were randomized to treatment with a combination of aranoza 600 mg/m^2 i.v. on days 1 and 2 plus cisplatin 100 mg/m^2 i.v. on day 1 repeated every 4 weeks, or to aranoza/cisplatin as above plus interferon alfa-n 3x106IU s.c. on days 3, 5, 7, 9, 11, 13, 15, 17 and 19. The results of treatment were similar in both groups; in each arm of 14 patients there was 1 complete response and 3 partial responses (RR: 21.4%). The best response was seen in patients with soft tissue and lymph node metastases. One patient each with lung metastases and liver metastases had partial remissions (21).

Aranoza was administered intraarterially in combination with cisplatin to 16 patients with disseminated skin melanoma of the extremities. A 2-h infusion of cisplatin 100 mg/m^2 (day 1) and aranoza 1000 mg/m^2 (days 2 and 3) resulted in complete response in 2 patients (12.5%)

Table V: Retrospective analysis of treatment in patients with stage III melanoma.

	Surgery + Aranoza	Surgery + DTIC	Surgery (control)
No. of pts	28	90	50
5-year overall survival	55.76 ± 10.4%	37.46 ± 5.78%	42.88 ± 7.75%
5-year relapse-free survival	43.46 ± 14.5%*	32.73 ± 5.56%	25.58 ± 7.83%*

*$p < 0.05$

and partial response in 7 patients (43.8%). The overall response rate was 56.3%. The limiting toxic effect was local skin toxicity. Other side effects included nausea and vomiting (100%), leukopenia (22%), hypertension (3.6%), allergic reactions (10.3%) and alopecia (37.9%) (21).

Combinations of aranoza with vincristine and cisplatin or dactinomycin were used in melanoma patients, resulting in a response rate of 30-33.3% stable disease in 22.3-30%. The median time to progression in responders was 7.6 months and the median duration of stable disease was 4.1 months. There were no unexpected toxic effects. Toxicity was reversible and included nausea and vomiting, grade 1-2 leukopenia, as well as grade 1-2 renal toxicity and neurotoxicity in patients administered platinum-containing combinations (22).

After several clinical studies confirmed the antitumor activity of aranoza in patients with disseminated skin melanoma, its use as adjuvant chemotherapy in operable melanoma patients was investigated. In one study, aranoza was given postoperativly to 28 high-risk (stage III) melanoma patients (T1-4N+M0). At this stage, the risk of relapse after surgical treatment is high, with over 50% of patients usually dying within 2 years after surgery (23, 24).

A retrospective analysis of 168 patients treated between 1982-1992 was conducted. Patients were divided into three groups: (1) 50 patients in whom only surgery was performed; (2) 90 patients in whom surgery was followed by 3 courses of DTIC 400 mg i.v. on days 1-5 every 4 weeks and (3) 28 patients in whom surgery was followed by 3 courses of aranoza 1000 mg i.v. days 1-3 every 4 weeks. All patients were followed up for 5 years. After 5 years, the overall survival and relapse-free survival in the surgery only group was 42.88 ± 7.73% and 25.5 ± 6.41%, respectively. In the DTIC-treated group, these values were 37.46 ± 5.78% and 32.73 ± 5.56%, respectively, and in the aranoza-treated group the respective values were 55.76 ± 10.4% and 43.46 ± 14.5%. The difference in the 5-year relapse-free survival between aranoza-treated patients and the control group was statistically significant (Table V). The results of this nonrandomized retrospective study indicate that aranoza used as adjuvant postoperative chemotherapy improved relapse-free survival at 5 years in a group of high-risk melanoma patients. In order to explore the possible role of aranoza in adjuvant postoperative chemotherapy in melanoma patients, additional prospective randomized studies are desirable.

Since clinical trials of aranoza in solid tumors other than melanoma (uterine sarcoma, breast cancer, head and neck tumors) showed some response, further clinical development with aranoza appeared to be justified. Aranoza was tested in patients with pancreatic, gastric and renal cancer without any significant clinical results (21). Studies in small cell lung cancer patients are in progress. A combination of aranoza 670 mg/m^2 i.v. on days 1 and 2, doxorubicin 40 mg/m^2 on day 1 and vincristine 4 mg/m^2 on day 1 was used as second-line chemotherapy in 15 patients with small cell lung cancer. Results showed 1 complete and 2 partial remissions (RR: 33.3%) among 12 relapsed patients sensitive to first-line chemotherapy. There were no responses in 4 refractory patients with tumor progression on first-line chemotherapy (25).

In conclusion, aranoza is a convenient and relatively well-tolerated nitrosourea derivative with a spectrum of antitumor activity typical for this group of compounds. At present it has been used as an established drug for the treatment of melanoma patients in the Russian Federation since 1996. Hopefully, further clinical trials will provide data necessary to extend indications for its clinical use.

Source

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