Revista Electrónica de Biomedicina
Electronic Journal of Biomedicine

ISSN: 1697-090X

Letters to the Editor / Cartas al Editor

ORAL ADMINISTRATION OF *BACILLUS OLIGONITROPHILUS* KU-1 MAY PREVENT SIDE EFFECTS OF CONVENTIONAL ANTICANCER TREATMENT

Sergey V. Malkov[1], Vladimir V. Markelov[2], Gleb Y. Polozov[1], Boris I. Barabanschikov[1], Maxim V. Trushin*[1, 3]

[1]Kazan State University, Department of Genetics [2] Kazan Municipal Rehabilitation Medical Health Center "Sanatorium Krutushka", [3]Kazan Institute of Biochemistry and Biophysics, Kazan, Russia.

mtrushin @ mail.ru

Rev Electron Biomed / Electron J Biomed 2006;2:105-107.

To the Editor:

Conventional chemotherapeutic and radiotherapeutic methods provoke significant side effects in cancer patients. Most of cancer patients show development of asthenia, anorexia, nail disorders, stomatitis, myalgia and dysgeusia as a result of anticancer treatment[1]. Some cancer sufferers demonstrate acute intestinal injury that is a common and serious problem leading to disruption of morphologic mucosal integrity and normal bacterial microflora and thereby favoring the malabsorption[2]. Hematologic abnormalities are, unfortunately, also frequent events in cancer patients[3]. In this connection, a search for efficient ways for cancellation of the above-mentioned side effects of conventional anticancer treatment is of great importance. We reported previously that oral administration of *Bacillus oligonitrophilus* KU-1 results in cancer inhibition[4]. Here we report that administration of the above-mentioned strain may prevent side effects of chemotherapeutic drugs and normalize blood picture.

Bacillus oligonitrophilus KU-1 (*Bacteria; Firmicutes; Bacilli; Bacillales; Bacillaceae*) strain was isolated from soil of Kazan city, Russia. 300 mg of soil was re-suspended in 2 mL of modified liquid medium of Alexandrov without potassium (pH 8.0) and inoculated on the agar plates with the same content and supplemented with orthoclase (g/L: 0.5). The full-grown mucilaginous colonies were checked on growth ability on liquid Alexandrov's medium without potassium and supplemented with orthoclase. Then *B. oligonitrophilus* KU-1 cells were grown at 20 0C without shaking during 2 days. Stationary phase *B. oligonitrophilus* KU-1 culture (0.5-1.0x10^9 cells per mL) was used for peroral administration according to a specially developed scheme[4].

We present here two cases where administration of *B. oligonitrophilus* KU-1 was in parallel with chemotherapy drugs. Case 1. Female was born in 1957. In late 1999, ovary tumor with metastases into liver and abdominal cavity as well as undifferentiated rectum tumor was revealed (T4NxM1).

In February 23, 2000, hysterectomy and resection of greater omentum were made at Government State Service "Oncology" (Kazan, Russia). Sigmostoma and rectum were not ablated. There was about 3 litres of ascitic fluid in the abdominal cavity. Right ovary was in the form of thick-walled cyst (20x18x15 cm). In the liver, there were three roundish formations (up to 3 cm in diameter). In the rectosigmoid section, there was Schnitzler's metastasis (2x3x1 cm). Urine analysis (May 5, 2000): weight - 1.010, pH 6.0, glucose and protein was absent. L. USI (March 31, 2000): liver - heterogeneous parenchyma near the edge of costal margin. There were hyperechoic formations (in SVI - 55 mm in diameter, in SVII - 41 mm in diameter). There were foci of disintegration in the center of each hyperechoic formation. In the left lobe of liver, there was hyperechoic formation (31 mm in diameter). Gall-bladder was increased. Ultrasound investigation (May 6, 2000): liver - variety of hyperechoic metastatic formations of 69 mm in diameter (some of them were with fluid inclusions). Kidneys, spleen, heart; lungs (according to X-ray examination) and pancreas were without pathology.

In May 2000, reception of *B. oligonitrophilus* KU-1 culture was started. The initial level of bacteria reception was 200 mL per day; since August and October, daily reception was increased up to 400 and 600 mL, respectively. Simultaneously, topotecan was received. Ultrasound investigation of liver (February 2, 2001): numerous metastases (47-123 mm in diameter). During all this time, the patient received daily 500-700 mL of *B. oligonitrophilus* KU-1 culture. Due to liver failure, the patient died in July 19, 2001.

Case 2. Female was born in 1962. In August 2002, double-sided ovary cystadenocarcinoma (4x4 and 5x7 cm) with a wide distribution into peritoneum was determined (T4NxM1). In addition, multiple metastases into the greater omentum were observed. Cystatin was received before the operation. In that period, the patient was very ill being. In August 20, 2002, hysterectomy and ablation of greater omentum were made at Samara Oncology Center (Samara, Russia). Since September 2002, until February 2003, the patient received *B. oligonitrophilus* KU-1 (300 mL per day). Increase in intracranial pressure was observed while blood pressure was normal. After CA125 normalization, bacteria were received with prophylactic aim (50 mL per day, a week of reception was changed by a week of interruption). In May 17, 2004, Ultrasound investigation revealed metastases into the cellular tissue of pelvis minor. Chemotherapeutic course of treatment (cystatin, 110 mg) was perceived very badly (there were retching and asthenovegetative syndrome). Since June 2004, the patient increased reception of *B. oligonitrophilus* KU-1 (300 mL per day). According to ultrasound investigation data, the size of metaplastic cancer in cellular tissue of pelvis minor decreased up to 30%. Now the patient continues to receive *B. oligonitrophilus* KU-1 (50 mL per day, a week of reception changes by a week of interruption). In January 2005, the patient was hospitalized due to relapse of thrombophlebitis. Clot was operated. The patient received antithrombin drugs. Since January 2005, reception of *B. oligonitrophilus* KU-1 was stopped. As a result, there was a significant increase in CA 125 level in March 2005. In April 23, 2005, reception of *B. oligonitrophilus* KU-1 was resumed (200 mL per day). State of health became significantly better until the middle of May 2005. In May 25, 2005, the patient died.

Beneficial effects of probiotic microorganisms for cancer patients are under intensive investigation not. It was shown by some researchers that, for example, Lactobacillus bulgaricus could be given to prevent radiation-induced enteritis[2]. The similar effects were observed during application of other probiotic strain called "Acilact" [5]. It is clear from the presented material that *B. oligonitrophilus* KU-1 may improve hematologic parameters in cancer patients (Table 1).

Table 1. Laboratory findings in cancer patients

Case #	Date of analysis and laboratory results
1	May 5, 2000: HGB 108, RBC 3.37, WBC 5000, BN 0.1, SL 58.6, MON 8.8, E 1.8%, LYM 30.7. TP 79.8, U 5.3, TB 4. TT 2.4, β-L 5.35. December 15, 2000: WBC 15100, RBC 2.7, HGB 79, HCT 23.3, PLT 597, PCT 0.551, MCV 86, MCH 29.2, MCHC 338, RDW 18.1, PDW 13.9, MPV 9.2, LYM 15.8, MON 5.9, GRA 78.3. CI 0.88. TSH 1.728, CA125 22.1 U/mL, CA72-4 3.8 U/mL. CEA 50x10^9/mL. January 15, 2001: WBC 17600, RBC 3.32, HGB 90, HCT 27.7, PLT 476, PCT 0.425, MCV 83, MCH 27.2, MCHC 326, RDW 17.6, PDW 13.8, MPV 9.0, LYM 8.5, MON 2.8, GRA 88.7. CI – 0.81. CA125 30.2 U/mL, CA72-4 25.6 U/mL, CEA >50x10^9/mL, CA19-9 >400 U/mL. January 17, 2001: G 5.14, ALAT 30.0, ASAT 70.2, TB 9.9, DB 4; CRP 9.29, GGT 518.8. January 31, 2001: WBC 15400, RBC 3.01, HGB 92, HCT 0.32, MCV 80.3, MCH 23.0, MCHC 286, RDW 21.5, LYM 13.5, MON 10.2, N 74.9, E 1.2, B 0.2. ESR 65, β-L 7.68, TT 0.8. TB 11.3. G 5.42, TP 81.8. February 6, 2001: WBC 10600, RBC 3.52, HGB 87, HCT 0.284, PLT 586, MCV 80.8, MCH 24.8, MCHC 308, RDW 20.6, MPV 7.4, BN 5, SL 80.0, MON 7, E 1.0, LYM 7. TT 0.8, β-L 7.68. AP 386.0, ALAT 35.6, ASAT 68.8, GGT 401, LDH 1473.9, TP 74.2, albumin 42.5 g/L, TB 8.8, G 4.88. March 16, 2001: WBC 10200, RBC 3.44, HGB 89, HCT 27.3, PLT 460, PCT 0.379, MCV 79, MCH 25.8, MCHC 324, RDW 16.9, PDW 12.3, MPV 8.2, LYM 17.7, MON 6.7, GRA 75.6. CI 0.78, ESR 45. TSH 3.692. G 4.37, ALAT 39.3, ASAT 74.7, TB 7.2, DB 4.5, C 7.32, alpha amylase 46.4 U/L, blood U 4.94, CRP 6.73, GGT 1041. CA125 419 U/mL, CA72-4 110 U/mL, CEA 2.0x10^9/mL, CA19-9 400 U/mL. April 7, 2001: HGB 92, ESR 68, WBC 9100, PLT 546. β-L 9.78, LDH 2186, GGT 799, ALAT 42.2, ASAT 96.3, G 6.54, albumin 44.6 g/L, TP 67.3, TB 11, AP 608, LYM 15.5, MON 9, N 72.7, E 2.1, B 0.7. May 22, 2001: ESR 60, WBC 12000, PLT 345. RBC 3.05, HGB 83, HCT 25.6, PCT 0.334, MCV 84, MCH 27.2, MCHC 324, RDW 18, PDW 13.7, MPV 9.7, LYM 11.7, MON 7.6, GRA 80. CI 0.82. serum albumin 28.64 g/L, G 3.73, ALAT 53.8, ASAT 353, TB 18.1, DB 13.8, C 5.96, AP 800, alpha amylase 22.2 U/L, serum iron 4.8 μmol/L, blood U 3.9, TP 73.2, CRP 191.9, GGT 712.3. CA-125 112.3 U/mL, CA72-4 110 U/mL, CA19-9 400 U/mL, CEA >55x10^9/mL.
2	August 27, 2002: ESR 15, HGB 128, RBC 3.93, WBC 4200, BN 2, SL 59, MON 8, LYM 28, E 3. TP 68.4, TB 7, CR 75, U 3.62, G 5.3. February 21, 2003: ESR 9, HGB 124, RBC 4.2, WBC 3500, PLT 190. BN 5, SL 62, MON 4, LYM 27, E 2. TP 72, TB 6.9. ALAT 0.6, PI 96.7, CR 92, U 5.17, C 5.7, G 3.8. CA125 30 U/mL. Autumn 2003: CA125 13 U/mL. December 5, 2003: CA125 11.4 U/mL. December 15, 2003: ESR 5, HGB 124, RBC 4.75, WBC 6400, PLT 280. BN 2, SL 52, MON 7, LYM 37, E 2. TP 61, ALAT 0.8, CR 55, U 4.4, C 7.1, F 4.75. April 5, 2004: ESR 8, HGB 131, RBC 4.46, WBC 4800, PLT 223. BN 2, SL 55, MON 9, LYM 34, E 0. TP 62.5, CR 70, U 3.39, C 7.3, F 5.25, PI 96.7, TB 6.9. April 13, 2004: CA125 12.8 U/mL. May 17, 2004, CA125 225 U/mL. June 4, 2004: HGB 128, RBC 4.18, WBC 4300, PLT 140. BN 0, SL 38, MON 15, LYM 47, E 0. TP 70, CR 96, TB 8.8 μmol/L, ASAT 6 U/L, ALAT 12. June 9, 2004: CA125 55.4 U/mL. July 12, 2004: ESR 12, HGB 133, RBC 4.55, WBC 5100, PLT 270. BN 2, SL 50, MON 9, LYM 34, E 5. TP 63, TB 10.3, C 7.3, PI 93.3, U 4.4, F 3.75. September 14, 2004: CA125 20.3 U/mL. March 2005: CA125 300 U/mL.
Abbreviations: HGB=haemoglobin (g/L), WBC=white blood cell (/μL), RBC=red blood cell (x10^9/μL), PLT=platelet (x10^9/L), HCT=haematocrit (%), PCT= (%), MCV=average volume of red blood cell (μm), MCH=average content of haemoglobin within the single erythrocyte (picogram), RDW=width of erythrocyte distribution in volume (%), PDW=width of platelet distribution in volume (%), MPV=median volume of platelet (μm), LYM=lymphocyte (%), MON=monocyte (%), GRA=granulocyte (%), CI=color index, MCHC=average content of haemoglobin within erythrocytes (g/L), ESR=erythrocyte sedimentation rate (mm/h), ALAT=alanine aminotransferase (U/L), ASAT=aspartate aminotransferase (U/L), TSH=thyrotropic hormone of hypophysis (μmol/L), CRP=C-reactive protein (mg/dL), GGT=glutamine transferase (U/L), LDH=lactate dehydrogenase (U/L), SL=segmentonuclear leukocyte (%), BN=band neutrophil (%), E, eosinophiles, L=lymphocytes (%) G=glucose (mmol/L), N=neutrophil (%), B=basophile (%), TB=total bilirubin (μmol/L), DB=direct bilirubin (μmol/L), TP=total protein (g/L), AP=alkaline phosphatase (U/L), PI=prothrombin index (%), CR=creatinine (μmol/L), U=urea (mmol/L), TT=thymol test (U), C=cholesterol (mmol/L), β-L=β-lipoprotein (g/L), D=diastase (U), F=fibrinogen (g/L).	

Despite application of chemotherapeutic drugs and cancer itself, both patients demonstrated normal hemoglobin levels, leukogram and biochemical values. Moreover, improvement of health state was observed despite harmful effects of chemotherapy. We consider that significant delay in lethal outcome was due to administration of *B. oligonitrophilus* KU-1. Although we reported about possible mechanisms of *B. oligonitrophilus* KU-1 action[6], the exact mode of the observed beneficial effects remains to be detected. Only one thing is a definite at present - *B. oligonitrophilus* KU-1 can be applied not only as therapeutic drug (that is more desirable) but also as adjuvant agent to suppress side effects of conventional anticancer treatments.

REFERENCES:

1. Martin M, Lluch A, Segui MA, Ruiz A, Ramos M, Adrover E, Rodriguez-Lescure A, Grosse R, Calvo L, Fernandez-Chacon C, Roset M, Anton A, Isla D, Del Prado PM, Iglesias L, Zaluski J, Arcusa A, Lopez-Vega JM, Munoz M, Mel JR. Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC): impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen. Ann Oncol. 2006;17:1205-12.

2. Demirer S, Aydintug S, Aslim B, Kepenekci I, Sengul N, Evirgen O, Gerceker D, Andrieu MN, Ulusoy C, Karahuseyinoglu S. Effects of probiotics on radiation-induced intestinal injury in rats. Nutrition 2006; 22:179-186.

3. Pujade-Lauraine E, Richard AJ, Sapede C, Hayward C. Erythropoietic agents in anaemic patients with cancer: a retrospective observational survey of epoetin alpha, epoetin beta and darbepoetin alpha use in routine clinical practice. Oncol Rep 2005; 14:1037-1044.

4. Malkov SV, Markelov VV, Polozov GY, Sobchuk LI, Zakharova NG, Barabanschikov BI, Kozhevnikov AY, Vaphin RA, Trushin MV. Antitumor features of *Bacillus oligonitrophilus* KU-1 strain. J Microbiol Immunol Infect 2005; 38: 96-104.

5. Budagov RS, Ul'ianova LP, Pospelova VV et al. The protective activity of a new variant of the probiotic Acilact in exposure to ionizing radiation and anticancer chemotherapy under experimental conditions. Vestn Ross Akad Med Nauk 2006; 2: 3-5.

6. Malkov SV, Markelov VV, Barabanschikov BI, Trushin MV, Marotta F. Genome rejuvenation and its applications. Biomed Scientist 2006; 50: 45-47.

Corresponding author: Dr. Maxim V. Trushin
Kazan Institute of Biochemistry and Biophysics
Lobachevskii str. 2/31, P.O. Box 30,
420111, Kazan, Russia
Tel.: +7843-2319026
Email: mtrushin@mail.ru

Received: July 5, 2006
Published: July 30, 2006