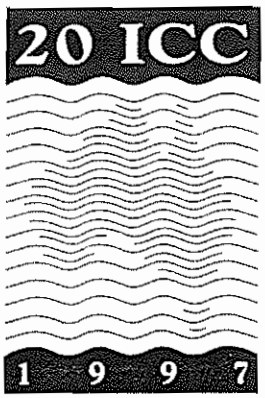

20TH INTERNATIONAL CONGRESS OF CHEMOTHERAPY

JUNE 29 - JULY 3, 1997
SYDNEY, AUSTRALIA

FINAL PROGRAMME & BOOK OF ABSTRACTS

13:30-15:30
ORAL PROFFERED PAPERS
OR02

Ukrain

MEETING ROOM 2

Chairs: Ronald Feld, Canada
John Grygiel, Australia

2076
Ukrain Induced Bimodal Cell Death in Wild-Type and Multidrug Resistant Cem Leukemia Cells.
P Hallock-Weerasinghe, S Hallock, Canada; Andrejs Liepins, Austria

2077
In Vitro Study of Apoptosis Induction By Ukrain.
S N Kurochkin, S I Kolobkov, Igor Votrin, Wassyl Nowicky, Austria

2078
Electron Microscopic and Morphohistochemical Analyses of Different Doses of Ukrain on Tumor Tissue of the Mammary Gland.
Konstantin Uglyanitsa, Wassyl Nowicky, Leonid Nefyodov, Austria; Witold J Brzosko, Poland

2079
Therapeutic Pathomorphosis in Rhabdomyosarcoma After Ukrain Treatment.
Yaroslaw M Susak, Ukraine; E R Deneka, Austria

2080
Effect of the Ukrain on bacterial Infections Under Experimental Conditions.
Wassyl Nowicky, Andrzej Denys, Ireneusz Ciebiada, Ewa Korczak, Austria

2081
Urinary Bladder Cancer and Ukrain
Witold J Brzosko, J Bortkiewicz, Poland; J W Nowicky, Austria

2082
Effectiveness of Ukrain on Melanoma.
Wassyl Nowicky, Yuriy Godysh, Austria

2083
Efficiency of Ukrain in Patients With Prostate Cancer
Konstantin Uglyanitsa, N Nechiporenko, Leonid Nefyodov, Austria; S R Krachkovskij; A S Karanik; A Karavaj, Belarus; Wassyl Nowicky, Austria; Witold J Brzosko, Poland

13:30-15:30
ORAL PROFFERED PAPERS
OR05

Drug-Resistant Pneumococci

MEETING ROOM 5

Chairs: Peter C Appelbaum, United States of America
Peter Collignon, Australia

2084
Penicillin Resistant *Streptococcus pneumoniae* in Denmark. A Nation-Wide Survey.
Jenny Dahl Knudsen, Lars V Pallesen, Helle B Konradsen, Henrik Westh, Denmark

2085
Streptococcus pneumoniae Resistance: An Epidemiological Survey in Austria in 1995.
Apostolos Georgopoulos, Astrid Buxbaum, Cornelia Moser, Ursula Straschil, Wolfgang Graninger, Austria

2086
Penicillin Resistant *Streptococcus pneumoniae*: A 1996 Comparison of Two Western Pacific Hospitals
Nichalas Nuttall, Australia; Donald J Lyon, Hong Kong; Joan L Faoagali, Narelle M George, Australia; Augustine F B Cheng, Hong Kong

2087
Prevalence of Penicillin-Resistant *S.pneumoniae* and Susceptibility to Antimicrobial Agents in Saudi Arabia
Atef M Shibl, A El-Rashid, A El-Bashir, K Osoba, Saudi Arabia; T Yasin, Philip J Masters, United Kingdom

2088
The Antibiotic Susceptibility of *Streptococcus pneumoniae* in the Middle East
Philip J Masters, United Kingdom; Ayad Al Ajeel, United Arab Emirates; Mohsen Al Rasheed, Saudi Arabia; Tulsi D Chugh, Kuwait; William L Dibb, United Arab Emirates; Ali Eibashire, Saudi Arabia

2089
Antibiotic Susceptibility of *Streptococcus pneumoniae* Strains Obtained from Respiratory Tract Specimens
Alda de Bartolo, Nicoletta Pagani, Francesco Blasi, Cristina Arosio, Tiziana Gazzola, Luigi Allegra, Italy

2090
Incidence of Penicillin-Resistant *Streptococcus pneumoniae* in Greek Children
Niki Fotopoulou, Sophia Tisplakou, Anthony N Maniatis, Panayotis T Tassios, Nicholas J Legakis, Greece

2091
Antimicrobial Resistance of Invasive *Streptococcus pneumoniae* in Slovenia, 1993-1996.
Milan Cizman, Metka Paragi, Nadja Jovan-Kuhar, Marija Gubina, Slovenia

2403

Combined Effects of SN-38 and Pentoxifylline on the Activation of Interleukin 1á-Converting Enzyme (ICE) Family Protease CPP-32, Through the Induction of Apoptosis in Pancreatic Carcinoma Cells

Ryushi Shudo, Hitoshi Ura, Akinori Itoh, Noriyuki Nishino, Takeshi Obara, Yutaka Kohgo, Japan

2404

Redistribution of Calcium and Iron Balance During Vanadium-Mediated Chemoprotection of Chemical Rat Hepatocarcinogenesis

Anupam Bishayee, Malay Chatterjee, India

2405

Effects of Danazol and Progesterone on Sex Hormone - Binding Globulin mRNA Expression in Human Endometrial Cancer Cell Line

Ryou Misao, Yoshihito Nakanishi, Jiro Fujimoto, Yasumasa Sato, Teruhiko Tamaya, Japan

2406

Bimodal Cell Death (BCD) Induced by Benzophenanthridine Alkaloids and Ukrain

Andrejs Liepins, Wassyl Nowicky, Austria

2407

Biological Response Modifying Properties of the Alkaloid Derivative Ukrain (NSC 631570).

Andrejs Liepins, Wassyl Nowicky, Austria

08.00:17:00
POSTERS
P007

Ukrain

POSTER AREA

5215

Apoptosis Induced by Ukrain in Patients with Breast Cancer
Witold J Brzosko, K Uglanitsa, K Fomin, J W Nowicky, Poland

5216

Modification of Antinociceptive Action of Ukrain by Agonists and Antagonists of Kappa-Opioid Receptors
Ewa Jagiello-Wójtowicz, Zdzislaw Kleinrok, Katarzyna Gustaw, Poland

5217

Effect of Ukrain on Protein Synthesis in Tumor and Liver of Tumor-Bearing Rats.
Leonid Nefyodov, Wassyl Nowicky, Konstantin Uglyanitsa, Belarus; B Fustochenko, Yuriy Godysh, Austria; Witold J Brzosko, Poland

5218

Blood Plasma and Tumor Tissue Proves the Efficacy of Ukrain Application in Breast Cancer
Leonid Nefyodov, Belarus; Konstantin Uglyanitsa, Belarus; Vladimir Smirnov, Yevgeniy Doroshenko, Austria; N Karavaj, A Karavaj, Belarus; Wassyl Nowicky, Austria

5219

Intensity of Glycolysis and Gluconeogenesis in the Liver of Tumor-Bearing Rats Administered with Ukrain.
Wassyl Nowicky, A Borodinsky, Konstantin Uglyanitsa, Yuriy Godysh, N Karavay, Leonid Nefyodov, Belarus

5220

Comparative Study of in Vitro Interaction of Ukrain and Other Cytostatics with Tissue Thiols of Guerin Carcinoma and its Cisplatin-Resistant Variant
Galina Kulik, Valentina Korol, Roman Bulkiewicz, Ukraine

5221

Antimetastatic Effect of Ukrain in Mice with Melanoma B-16.
Yaroslaw M Susak, Igor Todor, Sergey V Zemskov, Ukraine

5222

Influence of Ukrain on Oxygen Tension in Muscular Tissue of Melanoma B-16 Mice.
Yaroslaw M Susak, Igor Todor, Sergey V Zemskov, Ukraine

5223

The Study of Chronic Toxicity of Ukrain by Six Months Treatment in Rodents and Non-Rodents.
Yuri Furmanov, Inna Susak, Ruslan Zymbaluk, Serhiy Turchak, Austria

5224

Analysis of Efficiency of a Complex Treatment of Patients Suffering From Rectum Cancer
G Bondar; Alexander V Borota, Ukraine; Yu I Yakovets; Wassyl Nowicky, Austria; Kh V Baysheev; S E Zolotukhin

5225

Comparison of Neoadjuvant Monotherapies of Locally Spread Colon Cancer with Ukrain and 5-Fluorouracil
Volodymyr S Zemskov; Yaroslaw M Susak, Ukraine; Oleh Kravchenko; Sergey V Zemskov, Ukraine

THURSDAY

the distribution of metastatic cell burden among patients with subclinical disease.

The overall duration of therapy is important because the primary tumor initiates an accelerated regenerative response at some time during a course of cytotoxic therapy e.g. after 3-4 weeks in the average head and neck tumor treated with radiation therapy

Understanding the distribution of subclinical metastatic cell burden is important in evaluating the effectiveness of adjuvant chemotherapy of cancer.

Supported by PHS grant number CA-31612, NCI.

2074 CHEMO-RADIOTHERAPY FOR LUNG CANCER

David Ball. Peter MeCallum Cancer Institute, Melbourne, Australia

Non-small cell lung cancer (NSCLC). Since the NSCLC Collaborative Group meta-analysis revealed that the addition of cisplatin based chemotherapy (CT) to radiotherapy (RT) confers a small but significant survival advantage in patients with locally advanced NSCLC, ongoing studies have been designed to determine the optimum timing, duration and type of CT. Although induction CT *followed* by RT has been the most favoured approach, recent data suggest that sequential treatment may be inferior to concurrent CT/RT, but confirmation by randomised trials is required. RT using multiple fractions per day has also shown promise in NSCLC, and the feasibility of combining cis- or carboplatin with accelerated and hyperfractionated schedules has now been established.
Small cell lung cancer (SCLC) In patients with limited disease thoracic RT improves survival and it appears to be more effective the earlier it is given. Platinum based CT is preferred because of its compatibility with concurrent RT.
Conclusion. In an interesting example of convergent evolution, recent developments in the treatment of both NSCLC and SCLC have resulted in broadly similar approaches for both histologies. In both diseases combined RT/CT instituted early may improve survival by increasing local control and reducing the probability of distant metastasis.

2076 UKRAIN INDUCED BIMODAL CELL DEATH IN WILD-TYPE AND MULTIDRUG RESISTANT CEM LEUKEMIA CELLS

Liepins A, Hallock-Weerasinghe P, Hallock S, Memorial University of Newfoundland, St. John's, NF

Progress has been made in the treatment of cancers, such as malignant lymphomas, acute leukemias and certain solid tumors, i.e. testicular cancer and neuroblastoma. Unfortunately, the majority of patients that have initially responded to chemotherapy will relapse and die of their disease. The failure to respond to subsequent chemotherapy is supposed to be due primarily to the development of multidrug resistance (MDR). The principal mechanism responsible for the induction of multidrug resistance is due to overexpression of the MDR-1 gene and its product P-glycoprotein (PGP) on the tumor cell surface membrane. Thus, from the clinical standpoint, it is of great importance to find therapeutic agents or treatment modalities that will overcome the MDR phenomenon.
The present studies were undertaken to determine whether the alkaloid derivative Ukrain (NSC-631570) and the PKC-inhibiting alkaloid chelerythrene would overcome the MDR phenomenon in CEM-VLB 1000 cells in vitro. Results showed that these compounds, at a concentration of 2.0 to 32.0 ì µM (serial dilutions), were capable of inducing bimodal cell death with equal effectiveness in CEM leukemia wild type as well as in their MDR cell line expressed high levels of PGP on its cell surface membrane, thus demonstrating that PGP does not confer resistance to Ukrain and chelerythrene induced programmed cell death or apoptosis.

2077 IN VITRO STUDY OF APOPTOSIS INDUCTION BY UKRAIN 3

Kurochkin S, Kolobkov S, Votrin I, Nowicky W, Institute of Biological and Medical Chemistry, Russian Academy of Medical Sciences, Institute of Gene Biology, Russian Academy of Sciences, Centre of Medical Biotechnology, Ministry of Health, Moscow, Ukrainian Anti-Cancer Institute, Vienna

Aim: To study the ability of Ukrain to induce apoptosis in target cells, to elucidate sensitivity of different cell lines to Ukrain and to determine a particular cellular function affected by the drug.
Methods. Several cell lines of different origin were used: chinese hamster ovarian cell line (CHO); CHO cells with incorporated into genomic DNA multiple copy of recombinant human erythropoietin gene (k38); multi-drug-resistant (MDR) CHO; subclone of k38 cells resistant to Ethidium bromide, 10 ì g/ml (k38/12), Sp2/0 murine myeloma cell line; several hybridoma lines raised against different antigens and haptens; murine mammary gland sarcoma cells; non-metastatic (CSML) and causing lung metastases one (CSML-100); and some others. Cells were treated with Ukrain as well as with Etoposide in a range of 1-100 ì g/ml and with Colchicine, 1 ì g/ml.
Results: Ukrain possesses strong cytostatic activity and causes cell death via apoptosis within the same concentration range as Etoposide. In contrast to Etoposide, Ukrain exhibits lower efficiency on MDR CHO cells, and this decrease of activity correlates with resistance of cells to Colchicine. An unusual feature of Ukrain action is an inhibition of protein secretion by cells within first hours of their exposition to the drug. Verapamil and Cyclosporin A (Ca-channel blockers) cause lower effect on protein release. The combined treatment of cells with Ukrain and Etoposide demonstrates synergistic effect at lower concentration of both agents.
Conclusion: Ukrain induces apoptosis in vitro in a number of cell lines. Its efficiency is higher towards all sensitive cells and slightly smaller in case of MDR CHO cells than that of Etoposide. Due to observed synergistic effect of both drugs, it could be recommended to decrease effective doses for cancer treatment. The precise mechanism of inhibition of protein secretion by Ukrain is being studied.

2078 ELECTRON MICROSCOPIC AND MORPHOHISTOCHEMICAL ANALYSES OF DIFFERENT DOSES OF UKRAIN ON TUMOR TISSUE OF THE MAMMARY GLAND

Uglyanitsa K, Nefyodov L, Nowicky W, Brzosko W, Grodno Medical Institute, Institute of Biochemistry, Academy of Sciences of Belarus, Ukrainian Anti-Cancer Institute, Vienna, R. Brzosko Memorial Centre of Natural Medicine, Warsaw

This work summarizes the results of the morphologic study of tumor tissue obtained in 39 female patients with T2-3NO-1MO stages of breast cancer. Before the operation, the first group (13 patients) was intravenously injected with Ukrain (5 mg/day). The course included 10 injections with a total dose of 50 mg. The second group (13 patients) was injected with the drug in a dose of 10 mg/day, 10 injections with a total dose of 100 mg. The control group included 13 patients with breast cancer who had no chemo- or radiation therapy before the operation. Compared the control group, Ukrain, independently on the dose, induced changes in the cell nuclear cytoplasmic ratio and favoured the development of pronounced tumor cell polymorphism. The cytoplasma network was subjected to fragmentation. Most pronounced changes were found in mitochondria, especially when applying dosages of 100 mg of Ukrain. As opposed to the control group, Ukrain, in both of the doses, increased the number of fibroblasts and connective fibers in the tumor. The cytotoxic effect of the drug on the tumor tissue of the mammary gland was more pronounced when the total dose was increased from 50 mg to 100 mg.

2079 THERAPEUTIC PATHOMORPHOSIS IN RHABDOMYOSARCOMA AFTER UKRAIN TREATMENT

Deneka E, Susak Y, Bogomolets National Medical University, Kiev

Aim. To evaluate pathomorphosis of rhabdomyosarcoma after the treatment with Ukrain (chelidonine thiophosphoric acid derivative).
Methods: Five adult patients with rhabdomyosarcoma of skeletal muscles of different localization were treated with Ukrain, with a dose of 10 mg i.v. every second day, up to a total dose of 100 mg. The identical course of treatment was repeated after 10 days interval. An incision biopsy of the tumor was made before the treatment on every patient. After the end of the second course, i.e., after 10 days, the patients underwent an operation. No conventional chemotherapy nor an X-ray therapy had been made.
Results: Pathomorphosis of rhabdomyosarcoma can be described as follows. Tumor cells become monomorphic, compared to previous pleomorphism. The mitotic index decreases. The tumor tissue becomes rich in stroma, due to mature collagen. The number of cross striated cells increases. "Spider web cells" become smaller and nuclei

become pycnotic. Edamateous features are less expressed, the tissue becomes more «dry". Formation of colchicine mitoses were noticed in one case. In another case of rhabdomyosarcoma of a thigh, formation of pseudocapsule around the relapsing tumor was found. Proliferation and metastases of sarcoma during intervals between biopsy and operation were observed.
Conclusion: The described treatment of rhabdomyosarcomas with Ukrain can be evaluated as one that causes positive therapeutic pathomorphosis. This treatment is recommended for further evaluation.

2080 EFFECT OF THE UKRAIN ON BACTERIAL INFECTIONS UNDER EXPERIMENTAL CONDITIONS.

Ciebiada I, Nowicky W, Korczak E, Denys A, Military Medical Academy, Lodz, Ukrainian Anti-Cancer Institute, Vienna

Aim: Results of clinical observations show that bacterial and viral infections occur rather rarely in patients with cancer disease who were treated with Ukrain. The aim of our investigations was the evaluation of the antibacterial activity of Ukrain under experimental conditions in vitro and in vivo. The effect of Ukrain on the survival rates of infected mice, which were treated with antibiotics, was also investigated.
Methods: In order to evaluate the antibacterial activity of Ukrain in vitro, a method was used which is normally applied for the determination of Minimal Inhibitory Concentration (MIC) in relation to E. coli and S. aureus. In the studies in vivo, the influence of different doses and time of administration of Ukrain was evaluated, namely on the survival rate of Balb/c mice infected with lethal doses of E. coli or S. aureus. Afterwards, the animals received the most effective dose of Ukrain. The mice were infected as above and treated with different kinds of antibiotics in the following dosages: every 12 hours 7,5 mg/kg of Amikin (Bristol); 20 mg/kg of Cefobid (Pfizer), 75 mg/kg of Unasyn (Polfa). Then the survival rate of the mice was investigated.
Results: Ukrain had no antibacterial action in vitro. It increased the survival rate of infected mice, depending on the dose and the time of administration as well as on the kind of bacteria. It increased distinctly the survival rate of infected mice treated with Cefobid and slightly decreased the survival of mice treated by Amikin, but had no influence in the case of Unasyn.
Conclusion: Ukrain - like other stimulators - exerts differential influence on the survival rate of mice infected by bacteria and having been treated by antibiotics.

2081 URINARY BLADDER CANCER AND UKRAIN

Brzosko W, Bontkiewicz J, Nowicky J, Anti-cancer Studying Group, Warsaw

As presented before, Ukrain in therapeutic doses is selectively a cytostatic and cytotoxic drug, at the same time immunopotentiating human immunity. Both these properties make it almost unique among available at the present time anti-cancer therapeutics.
The present studies were carried out to evaluate the therapeutic efficacy of Ukrain in patients with bladder cancer. Five patients entered the study. They were diagnosed by routine procedure and classified as $T2N_0M_0$ bladder cancer cases. Clinical diagnosis and monitoring of the therapy was under histological, transrectal USG and cystoscopic control. Ukrain was injected intravenously in a dose of 10 mg every second day. In all patients tumors were eliminated by Ukrain treatment without surgical intervention. Depending on the case the amount of Ukrain which eliminated bladder cancer varied from 300 to 600mg of the drug and lasted from 3 to 6 months. Follow-up lasting in most of the patients from 6 to 12 months was negative for recurrence.

2082 EFFECTIVENESS OF UKRAIN ON MELANOMA

Nowicky W, Godysh Y, Ukrainian Anti-Cancer Institute, Vienna

In the National Cancer Institute, USA, in vitro studies have been carried out on melanoma, which have shown that Ukrain (NSC 631570-W/1) is very effective in the following melanoma tumor cell line subpanels: LOX IMVI, MALME-3M, M14, M19-MEL, SK-MEL-28, SK-MEL-5, UACC-257 and UACC-62. The mean values, $Log_{10}G150$:-5.70, $Log_{10}TGI$:-5.11, $Log_{10}LC50$: -4.56. Studies were also made by the European Organization for Research and Treatment of Cancer, which showed in vitro the cytotoxic activity of Ukrain (W122) against human tumor xenografts (HTX) on melanoma (MEXF 276/10/PO19GH). Ukrain proved to be effective in these grafts too.
In the years from 1983 to date, several patients received Ukrain as a monotherapy or together with chemo- or radiotherapy on out-patients basis. There were differing results: A patient, who already had melanine in the blood, was treated with Ukrain as monotherapy. He had a remission, which is lasting for more than 10 years already
In other patients only partial remissions were observed.
An interesting property of Ukrain is that it fluoresces in ultraviolet light in the relevant area. Which proves that Ukrain is accumulating in the tumor. These results were the cause for recognizing the necessity of arranging clinical studies on this subject.

2083 EFFICIENCY OF UKRAIN IN PATIENTS WITH PROSTATE CANCER

Uglyanita K, Nechiporenko N A, Nefyodov L, Krachkovskij S R, Karanik A S, Karavaj A V, Nowicky W, Brzhosko W, Medical Institute, Grodno, Institute of Biochemistry, Academy of Sciences of Belarus, Grodno, Ukrainian Anti-Cancer Institute, Vienna, R. Brzosko Memorial Centre of Natural Medicine, Warsaw

The randomized study included 20 patients with prostate cancer. The average age of the patients was 71 years (62-85 years). According to the histological structure, the tumors represented adenocarcinoma of different kinds. Before beginning and after cessation of the treatment, a comprehensive examination was carried out, including clinical biochemistry, hemopoiesis pattern, the amino acid pool in tumor tissue, sonography and CT of the prostate.
8 of 16 patients were treated with Ukrain, 10 mg daily, i.v., 100 mg/course. The repeated courses of Ukrain were carried out after a break of 7 to 10 days. In the control group were 10 patients treated conventionally.
There were no side effects of Ukrain, and no allergic reactions. It is characteristic that as early as after 2 or 3 Ukrain injections, all the patients noticed a considerable subjective improvement, improvement of sleep and a decrease of the number of night urinations. By the end of the Ukrain treatment course, all the patients noticed a disappearance of disuric disturbances as well as of colics and pains at urination. The urine stream became full and discontinuous.
The transrectal palpation of the tumor showed some decrease of the tumor and increase of its density. The ultrasound examination of the prostate showed an essentially unchanged size of the tumor, but its contours had became clearer, and according to the data of computer tomography, the optical density of the tumor had considerably increased. There were no significant changes in the parameters of the coagulogram, the hemogram and the biochemical tests after the Ukrain application.
The studies of the pool of blood plasma amino acid and their derivatives showed that the Ukrain treatment favored the abolition of amino acid imbalance, which is characteristic for prostate cancer. Therefore the data obtained on the application of Ukrain for prostate cancer showed the expediency of the application of Ukrain for these cases.

2084 PENICILLIN RESISTANT *STREPTOCOCCUS PNEUMONIAE* IN DENMARK: A NATION-WIDE SURVEY

Knudsen J, Pallesen L, Konradsen H, Westh H, Statens Serum Institut, Copenhagen

Denmark has for many years been a country with a prevalence of penicillin resistant *S. pneumoniae* (PRP) of les than 1%. Since May 1996, all isolates of PRP have been submitted to the Serum Institut for serotyping and a questionnaire has been sent to the patient and the patient's physician. During the first 6 month period 78 isolates were PRP. Nine isolates were from blood or CSF, median patient age 54 (range 1-81). 69 isolates were clinical isolates from 22 patients less than 3 years and 28 patients more than 60, median 34 years (range 1 month to 88 years). Type 9V and rough pneumococci were the most common serotypes with 8 serotypes responsible for 90% of the PRP. Questionnaires were returned from 51 patients/doctors. Nine of 26 cases of PRP may have been acquired abroad. Twenty-nine of 51 patients had received one or more antibiotics in the year prior to isolation of PRP. A full survey and results of a penicillin binding protein PBP 2B PCR, classifying the mutations responsible for penicillin resistance will be presented.

exert an effect on the expression of SHBG mRNA. Danazol and progesterone significantly ($p<0.05$) suppressed the expression of SHBG mRNA dose-dependently starting at a concentration of 10^{-6} and 10^{-8} M, respectively. Progesterone in a low concentration (10^{-10} M) with E_2 (10^{-8} M) significantly ($p<0.05$) increased the expression of SHBG mRNA, but danazol did not. In contrast, danazol and progesterone in high concentrations (10^{-6} to 10^{-5} M) with E_2 (10^{-8} M) significantly ($p<0.05$) suppressed its expression. The time course tudy showed the time-dependent decrease of SHBG mRNA level by danazol and progesterone (10^{-6}) with or without E_2 (10^{-8} M), except for a temporal increase by progesterone

These findings suggest that danazol and progesterone in a superphysiological milieu down-regulate the intracellular SHBG-related steroidal actions and that progesterone in a physiological milieu with estrogen up-regulates it in a hormone-dependent cell line.

2406 BIMODAL CELL DEATH (BCD) INDUCED BY BENZOPHENANTHRIDINE ALKALOIDS AND UKRAIN.

Liepins A, Nowicky W, Memorial University of Newfoundland, St. John's, Ukrainian Anti-Cancer Institute, Vienna

Selective induction of malignant cell death is one of the major goals of effective and safe chemotherapy. Recent developments in the understanding of programmed cell death (PCD) or apoptosis are expected to provide new leads for a safer chemotherapy. We have investigated whether the benzophenanthridine alkaloids or the thiophosphoric acid derivative Ukrain (NSC-631570) could induce PCD or apoptosis in human K562 leukaemia, HTLV and HIV infected cells. Results showed that the alkaloids chelerethryne, sanguinarine and Ukrain induced two distinct modalities of cell death programs. One modality corresponds morphologically to classical apoptosis or PCD characterized by blebbing and shedding of membrane vesicles with concomitant ^{51}Cr release. However, these alkaloid induced apoptosis was not associated with the characteristic nuclear DNA fragmentation. Higher concentrations of alkaloids and Ukrain induced a second cell death program, characterized by cell surface blister formation (BCD), high specific $_{51}Cr$ release and extensive DNA polyploidy. These two cell death programs are distinct from each other, in that they are interphased by a silent (SP) period, characterized by normal cell morphology and reduced specific ^{51}Cr release.

2407 BIOLOGICAL RESPONSE MODIFYING PROPERTIES OF THE ALKALOID DERIVATIVE UKRAIN (NSC 631570).

Liepins A, Nowicky W, Memorial University of Newfoundland, St. John's, Ukrainian Anticancer Institute, Vienna

Ukrain is a compound derived from Chelidonium majus alkaloids and thiophosphoric acid which has been found to be an immunomodulator in cancer patients and in AIDS patients with Kaposi sarcoma.

We investigated in vitro the immunomodulating properties of Ukrain using murine effector cell functions. Our results show that Ukrain activates the cytolytic function of spleen cells of C57B1/6 mice primed with allogeneic P815 cells when added directly to the CML assay medium. In the presence of 0.5 i g/ml to 2.0 i g/ml of Ukrain the cytolytic activity of spleen lymphocytes was increased from a background of ≤2.0% ^{51}Cr release to ≥50.0%, at an E/T ratio of 5:1 in a 3.5 hrs CML assay. Maximal response of spleen cell lytic activation by Ukrain was found to occur 18 days after alloimmunization.

The lytic activity of primed spleen cells cultured in low rIL-2 (10.0 U/ml/4 days) developed a lytic activity of 16.0% which in the presence of 0.5 i g/ml of Ukrain in the CML assay medium increased to ≥50%.

These results demonstrate that Ukrain can activate the lytic function of primed spleen lymphocytes directly by addition to the CML assay.

5213 DNA DAMAGE IN PERIPHERAL WHITE BLOOD CELLS IN NONSPECIFIC LUNG DISEASES BEFORE AND AFTER THERAPY WITH CEFPIROME

Karaulov A, Levchine I, Securenko S, Moscow Medical Academy, Institute of Biomedical Research and Therapy

It has been found that in 35-40% of patients with acute and chronic pneumonia, the DNA of peripheral blood mononuclear cells (PBMC) was damaged but these "spontaneous" were much lower as damages after therapy with tetracycline antibiotics. The same situation was observed during immunomonitoring. DNA damage in human peripheral white blood cells was measured using fluorometric method for rapid detection of DNA strand breaks of Birnboim H.C. and Jevcac J.J. (Cancer Res., 1981, 41, 1889). Peripheral blood mononuclear cells and neutrophil samples were obtained from 58 healthy control subjects and 48 patients with lung disease before and after therapy. We measured D value in orbitraty units. There was reverse correlation of D value and single strand breaks in nuclear DNA. After treatment with cefpirome the DNA damage of PBMC and the immune states did not significantly change and tendency toward normalization of this characteristic occurred 1 week after discontinuation of antibiotic therapy. It seems that "spontaneous" damages of PBMC of these patients exist as a result of reaction of these immunocompetent cells with bacterial antigens and such damages may be of great importance in the development of secondary immunodeficiency.

5214 PHAGOCYTOSIS AND KILLING OF AIDS ALVEOLAR MACROPHAGES (AMS) WITH AND WITHOUT RIFABUTIN (RBU).

Velluti G, Luppi F, Covi M, Moscara G, Bonucchi M, Pneumology-Policlinico, Modena

Previously we demonstrated an AMs phagocytosis and intracellular killing impairment in AIDS subjects, where RBU is prescribed for MAC infection therapy and prophylaxis. In 7 patients we studied those AMs activities against S. aureus ATCC 6538 without and with RBU at concentrations from 0.5 to 5 mcg/ml. AMs were put in contact with diluted RBU for 30' at 37°C. Then they were twice washed to remove the outside antibiotic and, after opsonization, were incubated with S. au. at ratio of 1:10. We added staphylolysin to kill the outside germs. After the AMs were lysed and the released bacteria were cultivated into BHIA plates for 18-24 hrs. From the colony's count we appreciated if the AMs phagocytosis increasing after RBU contact was due to cellular activation. The results are shown in tab. 1.

	No-RBU	0.5 mcg	1 mcg	2 mcg	5 mcg
Phagocytosis %	20 ± 5	41 ± 9	42 ± 12	41 ± 11	39 ± 10
Killing %	12 ± 6	34 ± 9	36 ± 13	35 ± 12	30 ± 12

$p < 0.0001$ comparing to no-RBU

RBU was able to increase, by unknown mechanism, AMs phagocytosis and killing either at therapeutic and at higher concentrations. This improvement seems useful to prevent not only MAC but also other opportunistic infections.

Supported by grants MURST chapter 40% n 95030802 and 60% n 95030801.

5215 APOPTOSIS INDUCED BY UKRAIN IN PATIENTS WITH BREAST CANCER

Brzosko W, Uglanitsa K, Fomin K, Nowicky J, International Cancer Study Group, Warsaw

Induction of programmed cell death, apoptosis, by Ukrain has recently been demonstrated in tissue culture in vitro.

The present studies were undertaken to evaluate if the mechanism of apoptosis is operational in elimination of malignant cells in patients with breast cancer treated with Ukrain. The studies were carried out on material obtained from patients with breast cancer who before mastectomy were treated with the drug. Ukrain was injected 10 x intravenously, one dose of 5 mg every second day, the last one 7 days before surgery.

Apoptotic cells were evaluated microscopically. It was found that Ukrain in a dose as low as 50mg was responsible for induction of apoptotic changes in cancerous cells the number of which varied in the treated patients and was proportional to the grade of histological malignancy of the tumor.

5216 MODIFICATION OF ANTINOCICEPTIVE ACTION OF UKRAIN BY AGONISTS AND ANTAGONISTS OF KAPPA-OPIOID RECEPTORS

Jagiello-Wojtowicz E, Kleinrok Z, Gustaw K, Dept Of Pharmacology, Medical University School, Lublin, Poland

Our studies indicated that the antinociceptive properties of Ukrain (4.75, 9.5 and 19 mg/kg i.p.) are modified by agonists and antagonists of kappa-opioid receptors. It was found that U 69593 (kappa-opioid agonist) enhanced or antagonized antinociception induced by Ukrain. Moreover, the nor-Binaltorphimine (kappa-opioid antagonist) completely antagonized the antinociceptive action of Ukrain in mice. The biochemical studies showed that Ukrain effectively displaced (^{3}H)-bremazocine from its cortical binding sites in a micromolar concentration range. Moreover, after the acute treatment with Ukrain, the density of (^{3}H)-bremazocine binding sites in cerebral cortex and brain stem was significantly decreased. Ukrain did not affect the affinity of (^{3}H)-bremazocine binding sites.

Our results suggested that the kappa-opioid receptor-mediated mechanism is involved in the antinociception induced by Ukrain in mice.

5217 EFFECT OF UKRAIN ON PROTEIN SYNTHESIS IN TUMOR AND LIVER OF TUMOR-BEARING RATS

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Cell malignancy is based on a disturbance in regulatory mechanisms of cellular differentiation and proliferation. A specific feature of tumor cells is their capacity of rapid growth and protein synthesis. Therefore, the effect of antitumor drugs on the protein synthesis is of great interest.

The experiments on 80 female and male Wistar rats, weighing 100-150 g and carrying implanted sarcomas M-45, were carried out to study the effects of the new anti-cancer drug Ukrain on the protein synthesis in vivo. The administration of the drug (0.02 mg/kg i.p. or into the tail vein over 14 days) was started after 1-7 days following the subcutaneous inoculation of the tumors

^{14}C-Leucine was administered i.p. to each group of the rats, in order to determine the activity of the protein synthesizing system. Tumor and liver were examined. Rats untreated with Ukrain served as control group.

Ukrain decreased the activities of translation processes in the tumor (up to 30% of the control group), but not in the liver cells. Most pronounced were the effects when Ukrain was given intravenously. High protein-synthesizing activity of liver and tumor polyribosomes was found in the tumor-bearing rats of the control group, as compared to that in the rats treated with Ukrain.

5218 BLOOD PLASMA AND TUMOR TISSUE PROVES THE EFFICACY OF UKRAIN APPLICATION IN BREAST CANCER

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It is known that tumors are capable of intensive amino acid accumulation from the organism of the tumor bearer. It has been proved that 75% of the amino acid pools in tissues and physiological fluids are formed by the degradation of endogenous proteins. Therefore the ration of essential to non-essential amino acid may serve as a significant criterion for protein catabolic processes. This is especially valid with respect to the increased level of lysine.

We have evaluated the regularities of the amino acid pool formation in blood plasma and tumor tissue of patients with T1-2N0M0 breast cancer, who were either untreated (25) or treated (25) with Ukrain (10 mg/day i.v., with a total dose of 50-100 mg). Patients who had to undergo radical mastectomy had Ukrain therapies before as well as after the operation.

The analysis of the complete pool of free amino acids and their derivates in blood plasma and tumor tissue of patients showed that the blood amino acid imbalance is having been normalized by Ukrain, the ratio of essential to non-essential amino acid was practically the same as that in healthy donors. After the Ukrain therapy, this ratio values in the tumor tissue were twice as high as those found in untreated patients. This increase may be due to high lysine, leucine and proline

concentrations, which indicates activation of the catabolic processes in the tumor under the influence of the drug. Thus, the processes of the blood plasma and tumor amino acid pools formation confirm the antitumor effect of Ukrain.

5219 INTENSITY OF GLYCOLYSIS AND GLUCONEOGENESIS IN THE LIVER OF TUMOR-BEARING RATS ADMINISTERED WITH UKRAIN

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Carbohydrate metabolism in the liver of tumor-bearing rats is characterized by prevalence of aerobic glycolysis and dramatic inhibition of gluconeogenesis. Changes in carbohydrates content in the body is a reflection of deficiency due to their enhanced utilization by growing tumor. Generally, the substrate both for glycolysis and gluconeogenesis is glucose-6-phosphate (G-6-P). We investigated the regulatory effect of the new anti-cancer drug Ukrain as a hexosephosphate-saving factor on the activities of hexokinase (HK), glucose-6-phosphatase (G-6-Ph-ase) as well as glucose and G-6-P content in the liver of 60 female and male Wistar rats weighing 100-150 g with implanted tumors, namely Walker-256, sarcoma M-1, sarcoma M-45, hepatocellular cancer PC-1. The administration of the drug (0.02 mg.kg i.p. or into the tail vein, over 7-14 days) was started after 1-7 days following the subcutaneous inoculation of the tumors, depending on their types. The growth of all the tumors studied was accompanied by a dramatic more than 3-fold increase in HK activity and a pronounced (2-fold) decrease in the G-6-Ph-ase rate in the liver of the animals in the experiment. The free glucose and G-6-P concentrations tended to decrease during intensive tumor growth.
The intraperitoneal administration of Ukrain normalized the HK and G-6-Ph-ase activities in the liver. Ukrain administered intravenously increases the level of free glucose. The intraperitoneal or intravenous administration of Ukrain to rats with sarcoma M-1 increased the activity of G-6-Ph-ase and reduced the G-6-P concentration. Ukrain injections to PC-1 bearing animals decreased HK and increased the G-6-Ph-ase activity.
Results: The increased HK activity and the decreased G-6-Ph-ase rate, which are of great significance for the primary phosphorylation of hexoses in tumor growth, are prevented by administration of Ukrain.

5220 COMPARATIVE STUDY OF IN VITRO INTERACTION OF UKRAIN AND OTHER CYTOSTATICS WITH TISSUE THIOLS OF GUERIN CARCINOMA AND ITS CISPLATIN-RESISTANT VARIANT.

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Ukrain is a semi-synthetic triophosphoric acid compound of alkaloid chelidonine possessing antitumour and immunomodulating activity.

Previously we had found that interaction of a number of antitumour drugs, such as thiotepa, cisplatin, doxorubicin, with tissue SH-groups plays an essential role in the mechanisms of their antitumor and toxic action.

To determine specific features of Ukrain mechanism of action we have carried out a comparative study of in vitro interaction of Ukrain, thiotepa and cisplatin with tissue thiols of liver, Guerin carcinoma and its cisplatin-resistant derivative. SH-group levels were assayed with the Elman technique.

The rate of Ukrain interaction with tissue thiols was found to be the same as that of thiotepa and cisplatin, which inhibit the growth of Guerin carcinoma by 95-98%. At the same time, Ukrain does not interact with SH-groups of liver tissue, while the other drugs cause decrease of thiol level in liver by 14-15%.

Tissue thiols of the tumour with acquired resistance to cisplatin do not interact with cisplatin, while their reactivity with Ukrain is higher than that of the parent tumour.

Conclusion: Ukrain posesses cytotoxic activity similar to that of known antitumour drugs, and, probably, can overcome tumour resistance to cisplatin.

5221 ANTIMETASTATIC EFFECT OF UKRAIN IN MICE WITH MELANOMY B-16.

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The antitumoral and antimetastatic action of Ukrain was studied on C57Bl/6 mice. The preparation was injected intravenously in the dose of 1 mg/kg every other day (total dose: 5 mg/kg), starting on the tenth day after tumour implantation into the muscles of one of the lower extremities, when there were already micrometastases in the lungs. In the control group the physiological solution was injected to animals. The effect of the preparation was evaluated by the determination of the primary tumor weight, the mean quantity of metastases and the mean volume per animal. Four days after cessation of the Ukrain therapy (23rd day after the tumor transplantation) the mice were killed for final examinations.
Results: Ukrain decreased the weight of the primary tumor by 20% ($p < 0.05$) in comparison to the control group. The mean quantity of metastases decreased by 33%, compared to the control group. The mean volume of metastases in animals of the group treated with Ukrain was by 80% smaller ($p < 0.5$) than in the control group. No metastases were observed in 3 (23%) mice of the group under investigation.
Thus, Ukrain in mice with transplantated metastatic melanoma B16 inhibits indeed the development of metastases in their lungs.

5222 INFLUENCE OF UKRAIN ON OXYGEN TENSION IN MUSCULAR TISSUE OF MELANOMA B-16 MICE

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The main aim of the paper was to study the influence of Ukrain on oxygen tension (pO_2) in the muscular tissue of melanoma B-16 mice. The pO_2 level was investigated by the polarographic method with open platinum electrodes. In order to study the rate of oxygen delivery and its uptake by musculus gastrocnemius, we used oxygen inhalation and tourniquet test. We started to inject Ukrain 10 days after the transplantation of melanoma, when there were already metastases in the lungs. 5 injections of Ukrain with 1 mg/kg on alternate day (total dose: 5/mg/kg) were given. After the 1st injection (11 days after the transplantation) there was a distinct tendency to an increase of the oxygen saturation by the muscle during inhalation and to its delivery during the tourniquet test. After the 5th injection of Ukrain (19 days after the tumor implantation) the level of oxygen tension in the muscular tissue and the rate of oxygen delivery was distinctly higher ($p<0.05$) than those in the untreated animals.
Result: Ukrain improves the oxygen metabolism in the muscular tissue of the animals with implanted metastatic melanoma B-16.

5223 THE STUDY OF CHRONIC TOXICITY OF UKRAIN BY SIX MONTHS TREATMENT IN RODENTS AND NON-RODENTS

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Aim: To study chronic toxicity of Ukrain (NSC 631570) in rodent and non-rodent mammalian animals in six months administration of the drug.
Material and methods: Two studies were carried out. Rodents: rats, 4 groups, 40 animals (20 female and 20 male) in each group. Non-rodents: rabbits, 4 groups, 12 animals (6 female and 6 male) in each group. Groups 1 of both species were control groups. Groups 2-4 were treated with Ukrain injections in dosage of 0.7, 0.3 and 0.07 mg/kg BW respectively, injections on alternate days during 6 months, intramuscular in rats and intravenous in rabbits. Control groups were treated with normal saline solution in equivalent dosage and in the same way as the experimental groups. Toxicity was studied according to developed protocol.
Results: No significant difference of clinical, hematological, biochemical and histological parameters between experimental and control groups of animals was found as well as no significant difference between values on the beginning and at the end of the studies. According to WHO criterions the toxicity of Ukrain was grade 0. A possible reason for it could be the high value of Ukrain's therapeutic index: 1250.

5224 ANALYSIS OF EFFICIENCY OF THE COMPLEX TREATMENT OF PATIENTS SUFFERING FROM THE RECTUM CANCER

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Randomized investigation of treatment of 48 patients suffering from the rectum cancer at stages: T_{3-4} N_{0-3} M_0 was performed in the Clinic of Proctology of the Donetsk Regional Anticancer Center. It was compared the effectiveness of complex therapy that consisted of following means: I group intensive course of the high-fractional X-ray therapy in combination with the direct protracted endolymphatic chemotherapy with the fluorouracil at cumulative dose of 5g + surgical operation; II group - monotherapy with Ukrain: 10 mg intravenously each second day up to 60 mg + surgical operation + 40 mg of Ukrain in postoperative period. In 24 patients (mean age 58.3 years old) without expressed attendant pathology were included into both groups. Each one patients was examined before treatment and control dynamic investigation was routinely performed after the above mentioned types of therapy. Besides instrumental examinations it were carried out assessment of some clinical and biochemical parameters and detection of the immune system state (IgA, IgM, IgG; T - and B-lymphocytes numbers, phagocytic activity; CIC; AFP; CEA).

Practically no toxic effects were found after Ukrain monotherapy while in case of the chemo-radiation therapy it were obvious well expressed objective and subjective signs of intoxication. Noteworthy, that Ukrain monotherapy was found to result in elevated T- and B-lymphocytes numbers and immune globulins content, and increased phagocytic activity. Although, tumor regression was practically equal in both patients groups (18 and 24% respectively), the expressiveness of morphological changes was substantially higher after Ukrain monotherapy. During surgical operation the technical difficulties occurred oftenly in patients received chemo-radiation therapy. Occurrence of postoperative inflammatory complications was substantially higher in I group (35.6%), than in II-group (11.6%). During nine-months observation over patients of both groups it were distinguished 5 cases of tumor process relapse in patients of I group and I case - in II group.

5225 COMPARISON OF NEOADJUVANT MONOTHERAPIES OF LOCALLY SPREAD COLON CANCER WITH UKRAIN AND 5-FLUOROURACIL.

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Aim: To improve the results of treatment of the locally spread colon cancer using monotherapy with Ukrain in the combination with operative treatment.

Methods: To devitalize the tumor before the operation we have administered Ukrain to 38 patients with locally spread colon cancer (T3-4 N0-1 M0) every second day 10 mg intravenously, with a total dose of 100 mg and 20 mg, immediately before the operation. The control group (also 38 patients) received 5-Fluorouracil in a dose of 600 mg/m² (total dose 5.5 - 6.0 g) per course. The treatment was continued in the postoperative period, using the identical schemes.

Results: In the group treated with Ukrain, we observed a distinct ($p<0.05$) decrease of tumor markers AFP, CEA and CA-125, and a stimulation of the immune system. The survival rate within 3 years was 65.7%.

Conclusion: Ukrain may be used in a complex therapy for locally spread colon cancer.

5226 ELECTRON MICROSCOPIC OBSERVATIONS OF EPITHELIAL CELLS OF THE BRONCHI BEFORE AND AFTER ADMINISTRATION OF CLARITHROMYCIN IN SINOBRONCHITIS PATIENT

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The macrolide antibiotics are drawing attention for its actions other than antibacterial activity, and its mechanism is under investigation.

We conducted electron microscopic observation of epithelial cells of the bronchi before and after administration of clarithromycin (CAM) in sinobronchitis patient and reviewed the changes.

The subject was 63 years old, male, sinobronchitis patient with persistent coughing, sputum, and shornesss of breath during exertion. 400mg/day CAM was administered for 3 months, and epithelial cells of the bronchi were collected by transbronchial biopsy and were observed under electron microscope.

Before administration, cilia have fallen out and were nearly absent, secreted mucus were seen in the intercellular space, and secretion was extremely accelerated. After administration, the cilial epithelia improved dramatically almost to normal condition.

It is interesting to observe such change in epithelial cells of the bronchi in severe sinobronchitis patients after 3 months of CAM administration with improvement of clinical conditions.

5227 IN VITRO EFFECT OF AZITHROMYCIN ON *S. PNEUMONIAE*

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It is known that over extended periods of time subinhibitory concentrations of antibiotics in vitro can lead to the development of resistant bacteria. Due to the long tissue half-life of azithromycin (AZ), subinhibitory concentrations of AZ are observed at the site of infection until the antibiotic is completely eliminated.

This study analyzed the effect of AZ on *S. pneumoniae* when exposed in vitro over a period of 30 days. To do so, we added one strain of *S. pneumoniae* to 0.1i g/mL AZ in liquid broth and cultured daily. On Day 9, a gradual increase in resistance from 0.1i g/mL to 0.3i g/mL was observed, and on Days 9-12, resistance increased dramatically from 0.3i g/mL to >128 MIC. On Day 14 resistance had increased to >256 MIC and the microorganism was removed from the AZ broth and added to an antibiotic-free broth. This resulted in a decrease in resistance for the next 10 days. On Day 26 the microorganism was added to 0.01i g/mL AZ in liquid broth and, unlike the previous trial, within two days (vs. 9-12 days), strong resistance again emerged.

These results suggest that the long half-life of AZ, and the resultant low levels of antibiotic at the site of infection, may contribute to the development of resistant microorganisms, including *S. pneumoniae*.

5228 ACTIVITY OF CLARITHROMYCIN, CEFOXITIN, AMOXICILLIN ± CLAVULANATE AGAINST 160 ANAEROBES CAUSING CHRONIC ENT INFECTIONS

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Treatment of chronic head and neck infections usually consists of cefoxitin or amoxicillin/clavulanate. Recent studies with methods which avoid CO_2-induced lowering of the pH have shown clarithromycin to be active against most non-B. fragilis group anaerobes. This study used agar dilution MIC to test activity of clarithromycin, cefoxitin, amoxicillin and amoxicillin/clavulanate against 160 anaerobes implicated in chronic ear, nose and throat infections. For cefoxitin and amoxicillin/clavulanate, standard NCCLS agar dilution was used, and for clarithromycin the Oxyrase method (consisting of adding Oxyrase [an O_2-scavenging enzyme] + substrates to standard MIC medium in special OxyDishes with lids, and incubating plates in air), or incubation under CO_2 at pH 8.0. $MIC_{50}/_{90}$s (µ/ml) were as follows:

Group	Clarith	Cefoxitin	Amoxic	Amox/clav
Prevo/Porphyr(52)	.06/.5	1/16	1/128	≤1/1
F.nucl/necro (17)	8/16	.25/2	≤.12/128	≤.12/.25
F.mortif/var (20)	>64/>64	4/8	2/32	2/8
Peptostrep (50)	1/4	.25/8	.25/16	≤.12/16
G+ nonsp rods (21)	0.16/.12	.5/64	.25/1	.25/1

The only strains yielding clarithromycin MICs ≥32 µg/ml were F.mortiferum and F. varium, both rare human pathogens. There are currently no NCCLS approved macrolide breakpoints for anaerobes. However, this study indicates that, at MIC ≤16.0 µg/ml (levels achievable in vivo), clarithromycin shows promise in treatment of chronic ENT infections in which anaerobes may play a part.

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