USEFULNESS OF ALKALOIDS IN TREATMENT OF CANCER. PART 2: USE OF ALKALOIDS, SENSITIZING ACTIVITY, ANTIMETASTATIC ACTIVITY, SIDE EFFECTS, CHEMOPROTECTIVE ACTIVITY AND RUNNING CLINICAL TRIALS

*Anna Och[1], Marek Och[1], Janusz Kocki[2], Anna Bogucka-Kocka[1]**

[1]Department of Pharmaceutical Botany, Medical University of Lublin, Lublin, Poland; [2]Department of Clinical Genetics, Medical University of Lublin, Lublin, Poland

*Corresponding author e-mail: anna.kocka@tlen.pl

Summary. In the previous part of the review the authors have presented the mechanisms of the anticancer selected alkaloids activity. The discovery of these mechanisms resulted in the introduction of the disclosed compounds for the cancer treatment. In this section the alkaloids use in the treatment of the patients with various types of cancer, as well as the accompanying side effects are described. The stage of running clinical trials, which provides some information on the latest treatment options of using the disclosed compounds is presented. The chemoprotective and sensitizing activity of alkaloids which is described in the article is very important and promising. Also, the ability of inhibition tumor metastasis is characteristic for these compounds, which is also given to the presented part of the article.

Key words: alkaloids, sensitizing activity, antimetastatic activity, side effects, chemoprotective activity, clinical trials.

USE OF ALKALOIDS IN TREATMENT

Indicine N-oxide treatment gives responses in the cases of colon carcinoma, refractory leukemia and acute leukemia [25]. This compound is found to be effective in leukemias and other types of tumor but dose-dependent toxicity is a limiting factor, especially in children tumors. Nonetheless, indicine N-oxide was used in treating children with malignant solid tumors: osteosarcoma, neuroblastoma, brain tumor and other miscellaneous tumors.

As regards clinical usage of noscapine, it increases survival in temozolomide-resistant gliomas [20], in the cases of leukemia it suppresses cell proliferation [43] and it limits tumor growth and lymphatic metastasis of PC3 human prostate cancer [2]. The cases of non-Hodgkin's lymphoma, chronic lymphocytic leukemia and glioblastoma were also examined in clinical trials with noscapine [33]. As regards in vitro trials, it has been shown that noscapine induces apoptosis in myeloid leukemia cells HL60 and K562 cell lines [16, 19, 23].

In combined treatment noscapine showed synergistic effects while combined with known anticancer drugs. Alkaloid sensitizes leukemia cells and myeloma cells to tumor necrosis factor and chemotherapeutic agents. It is due to its ability to suppress the NF-kB signaling pathway [43]. Noscapine in combination with gemcitabine gives therapeutically beneficial effects. In non-small cell lung cancer such treatment decreases the cell survival proteins expression, VEGF, and microvessel density and enhances DNA fragmentation. Also the increase in cleaved caspase 3 levels is observed [6, 7, 8]. Positive effects are also observed with doxorubicin. In triple negative breast cancer cell lines MDA-MB-231 and MDA-MB-468 combined treatment decreases the NF-kB pathway proteins expression, VEGF and cell survival. They together increased apoptotic expression and growth inhibitory proteins [7]. Noscapine is able to sensitize chemoresistant ovarian cancer cells to cisplatin [19]. Such combination treatment is also found to be effective in A549 and H460 lung cancer cells, where it results in the highest increase in percentage of apoptotic NSCLC cells and increases the expression of p53, p21, caspase 3, cleaved caspase 3, cleaved PARP and Bax. What is more, it decreases the expression of Bcl-2 protein and

surviving proteins compared with the treatment with either the agent. This treatment decreases the proteins expression of pAkt, Akt, cyclin D1, survivin, PARP, Bcl-2, and increases the proteins expression of p53, p21, Bax, cleaved PARP, caspase 3, cleaved caspase 3, cleaved caspase 8, caspase 8, cleaved caspase 9 and caspase 9 [8].

Noscapine also appears to be a chance for patients treated with radiation. The alkaloid significantly increases tumor growth delay, causes a decrease in BrdU incorporation, increases apoptosis in combination with radiation. It also enhances the GL261 glioma tumors sensitivity to radiation [34, 35]. Chemotherapy with noscapine in patients with relapsed or refractory multiple myeloma is assessed by the National Cancer Institute [32].

Vinblastine is a compound used in chemotherapy courses composed, for example, of doxorubicin hydrochloride, bleomycin sulfate and dacarbazine followed by involved- nodal radiotherapy. The compound is used beside dacarbazine and beside adriamycin in people with Hodgkin's lymphoma and is also included in the PVAG- prednisone, vinblastine, doxorubicin and gemcitabine course [32].

It has been proved that prednisone, vinblastine, doxorubicin and gemcitabine are safe and feasible in elderly HL patients [4]. Temsirolimus/vinblastine combination induced a significant and sustained antitumor activity, with an effective reduction in tumor vessel density in both Huh7 and Hep3B xenograft models by the downregulation of several key anti-apoptotic/ survival proteins (survivin, Bcl-2, and Mcl-1) [52]. A promising role of gryzeofulvin in breast cancer combination chemotherapy was described [37].

Vincristine is a chemotherapeutic drug possessing probably the most of all usages and combined with many drugs during courses. It is still very intensively examined in many clinical trails.

Vincristine is contained in standard chemotherapy composed of vincristine, dactinomycin and ifosfamide in tumors of Ewing's family. Vincristine is a component of adjuvant chemotherapy in early stage follicular lymphoma. The combined treatment efficacy was evaluated in patients with untreated mantle cell lymphoma, where vincristine is combined with cyclophosphamide, doxorubicin and prednisone. Vincristine is a compound evaluated in NCI immunochemotherapy comprising rituximab, cyclophosphamide, doxorubicin hydrochloride and vincristine in patients with previously untreated, low-risk, aggressive B-cell non-Hodgkin's lymphoma. The study is run with patients with histologically confirmed aggressive B-cell non-Hodgkin's lymphoma, including the following subtypes: grade 3 follicular lymphoma, diffuse B-cell lymphoma, including diffuse large cell lymphoma with any of the following variants: centroblastic, immunoblastic, plasmablastic, anaplastic large cell, T-cell-rich B-cell lymphoma; primary effusion lymphoma, intravascular B-cell lymphoma, primary mediastinal B-cell lymphoma, Burkitt's or Burkitt-like lymphoma, mantle cell lymphoma (blastoid) and aggressive marginal zone lymphoma (monocytoid). Wilms' tumor, rhabdomyosarcoma, acute lymphoblastic leukemia, or non-Hodgkin's lymphoma are examined in young patients [32].

The next combination examined is chemotherapy comprising vincristine, etoposide, cyclophosphamide, and cisplatin with or without high dose methotrexate and leucovorin calcium followed by consolidation chemotherapy comprising carboplatin and thiotepa and peripheral blood stem cell rescue assessed in pediatric patients with newly diagnosed supratentorial primitive neuroectodermal tumors or high-risk medulloblastoma [32].

Vincristine is used in the treatment of patients with poorly differentiated neuroendocrine carcinomas representing highly malignant tumors with an immense tendency to metastasize and with a poor prognosis. The treatment consists of palliative chemotherapy and corresponds to the treatment of extensive stage small cell lung cancer. The therapy with vincristine combined with carboplatin and etoposide has also been evaluated [36].

Vincristine as a component of chemotherapy composed of etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin for recurring and refractory extranodal natural killer/T-cell (NK/T) lymphoma, resistant to cyclophosphamide, doxorubicin, vincristine and prednisone therapy gave promising outcomes [18].

At a mean of 11 years, 4% of children with germline retinoblastoma treated with carboplatin, vincristine and etoposide as frontline therapy developed second malignant neoplasms. No second malignant neoplasms were found in non-germline patients [45]. The combination of VE-465 and vincristine increased the levels of cleaved caspase 3, cleaved caspase 7, cleaved caspase 9, cleaved PARP and Phospho-Chk2, suggesting that the combination caused Chk2-mediated activation

of the G2/M checkpoint, resulting in sequential apoptosis induction. The combination markedly decreased the Phospho-ERK1/2 level, suggesting that the combination alters a cellular signaling pathways network in the myeloid leukemia cells [49]. It has been established that the vincristine chemotherapeutic activity is potentiated by crocetin [51].

Vincristine is a component of chemotherapy for the high-risk gestational trophoblastic neoplasia treatment. This therapy was found to be highly effective for the management of high-risk gestational trophoblastic neoplasia, and the toxicities were minimal. The reproductive outcome after the treatment was excellent [11].

A combination of clodronate with vincristine has been examined and was found to elicit synergistic killing associated with a significant increase in the cell cycle arrest of canine malignant histiocytosis-an aggressive neoplasm of macrophages and dendritic cells, which gives a chance in gliomas treatment [15]. It is used parenterally in acute leukemias in children [39].

L-asparaginase, vincristine and prednisone combined with radiotherapy are the safe and effective treatment for localized nasal natural killer/T-cell lymphoma [21].

Colchicine used in the binary combinations of the platinum compounds: cisplatin, oxaliplatin , YH12 and TH, with colchicine applied to A2780 and A2780(cisR) ovarian cancer cell lines shows sequence- and concentration-dependent synergism [50]. Also, benomyl and colchicine synergistically inhibited the HeLa cells proliferation and blocked their cell cycle progression at mitosis; benomyl and colchicine bind to tubulin at different sites so that the colchicine binding seems to positively influence the binding of benomyl to tubulin and vice versa [9].

Quinine does not improve the survival of adult patients with de novo acute myeloblastic leukemia, even though it improves the complete response rate in a small subgroup of patients defined by rhodamine 123 efflux. In combined chemotherapy with cyclophosphamide, vincristine, doxorubicin, dexamethasone quinine does not appear to be a promising therapy with respect to improved response or OS in intermediate- and high-grade advanced-stage non-Hodgkin's lymphoma [29, 32]. There has been also reported the efficacy of using quinine in combination with cyclophosphamide, vincristine, adriamycin, and dexamethasone (CVAD) chemotherapy in the treatment of advanced breast cancer [44].

SENSITIZING ACTIVITY

The rate of adriamycin and dexamethasone sensitization by verapamil and quinine has been assessed as 19% [44]. Quinine induces an accelerated distribution of epirubicin from the blood into the tissue [12]. It is used with verapamil in patients with intermediate- and high-grade non-Hodgkin's lymphoma as a second chemosensitizing agent [32]

MULTIDRUG RESISTANCE

An important fact concerning vinblastine treatment courses is that it is downregulated with cobalamine as regards mdr-1 gene expression, as well as Pgp expression and function, and cobalamine significantly increases cytotoxicity of vinblastine [1, 28, 46].

Colchicine is not effective in cases of multidrug resistance. A combined effect of P-glycoprotein and multidrug resistance-associated protein 2 dominated colchicine transepithelial transport, leading to the complete coverage of the entire small intestine, and made the efflux transport dominate the intestinal permeability process in breast cancer cells [13].

Quinine seems to be the greatest hope for MDR cases. This agent inhibits the drug efflux pump P-glycoprotein which is overexpressed in multidrug resistant tumors and may improve the efficacy of some antineoplastic agents [32]. It is a reversal agent and inhibitor of the multidrug resistance pump [48]. When malignant cells occur to be positive for P-glycoprotein, quinine is administered orally and added to chemotherapy. Quinine given with mitoxantrone increased the complete response rate and survival in P-glycoprotein positive myelodysplastic syndromes cases treated with intensive chemotherapy in patients with high risk myelodysplastic syndromes. Quinine had no effect on the response rate and survival of P-glycoprotein negative myelodysplastic syndromes [47]. Sera from quinine-treated patients with relapsed or refractory acute myeloblastic leukemia, relapsed or refractory acute lymphoblastic leukemia, secondary acute leukemia or blastic transformation of myelodysplastic syndrome or myeloproliferative syndrome showed increased mitoxantrone uptake in multidrug resistance -positive cell lines [40].

Quinine had a weak effect on doxorubicin accumulation in human erythroleukemia cell line K562 but was able to completely restore doxorubicin sensitivity in these resistant cells. Quinine was not able to decrease azidopine binding to P-glycoprotein, it had essentially intracellular targets involved in drug redistribution from sequestration compartments. This alkaloid modified the intracellular tolerance to doxorubicin, which suggested its ability to modify drug distribution within the cells. It acted principally on doxorubicin redistribution within the cells, allowing the drug to reach its nuclear targets [3]. It was suggested that the quinine oxidized metabolite was a more potent inhibitor of the multidrug resistance pump than was the parent compound. In CEM/VLB100 cells treated with rhodamine 123, quinine-10,11-epoxide was approximately 8- fold more potent than quinine [48]. Quinine induced a dose-dependent increase in doxorubicin uptake in the multidrug resistant human leukemic K562/ADM cell line while it had a slight effect on mitoxantrone and no effect on vincristine uptake [14]. It was determined in NCI that quinine exerted a chemosensitizing effect on paclitaxel in paclitaxel-resistant patients with non-Hodgkin's lymphoma. NCI evaluated VAD-P- vincristine, doxorubicin, dexamethasone, prednisone chemotherapy with quinine as a drug resistance reversal agent in previously untreated multiple myeloma. The ability of quinine as a P-glycoprotein binding agent to reverse multidrug resistance in AIDS-related and HTLV-I-related non-Hodgkin's lymphoma was also assessed [32]. Quinine did not increase nuclear anthracycline uptake in multidrug-resistant Chinese hamster ovary LR73 cells; it induced an increased in MDR1 gene expression in these cells. Quinine was unable to significantly increase nuclear pirarubicin uptake in multidrug-resistant K562R and CEMR human leukemic cell lines. The effect of quinine on MDR1 gene expression was dependent on the cell line studied. Quinine could modify the molecular environment of anthracyclines and/or their binding to a possible cytoplasmic target [31].

Quinidine, used as Chinidinum sulfuricum, is a reversal agent and inhibitor of the multidrug resistance pump [14]. Quinidine is a blocker of mdr-1-coded efflux pump activity [32]. It significantly increased the cytotoxicity of paclitaxel in P-glycoprotein-positive MES-SA/DX5, but not in the P-glycoprotein-negative MES-SA cells at nontoxic concentrations. Quinidine effectively enhanced the accumulation of a P-glycoprotein substrate, rhodamine in paclitaxel -treated MES-SA/DX5 cells. In addition, quinidine effectively cleaved poly (ADP-ribose) polymerase, activated caspase-3, and downregulated P-gp expression as well as increased sub-G1 apoptotic portion in paclitaxel -treated MES-SA/DX5 cells [24].

ANTIMETASTATIC ACTIVITY

Noscapine can be important as regards metastasis as it possibly possesses antiangiogenic activity. This activity is associated with decreasing HIF-1alpha expression in hypoxic tumor cells. Also, target genes upregulation, such as vascular endothelial growth factor, is decreased, which is associated with angiogenic activity. Noscapine can also act by inhibiting endothelial cells from forming blood vessels in response to the vascular endothelial growth factor stimulation [33]. Noscapine is able to stop the disease progress also by conjunction with the foliate receptor. It combines at C9 with the foliate a receptor in SKOV3 and A2780 ovarian cancer cell lines [41]. It promotes the degradation of cobalt stabilized HIF-1 a protein in ovarian cancer cells [26, 27].

Chemotherapy using vincristine, etoposide, and carboplatin occurred to be effective in preventing metastasis in every case (100%) in patients with high risk retinoblastoma [22].

The treatment of Co26 and Co51 colon cancer cells with colchicine inhibits pressure-stimulated cell adhesion to murine surgical wounds and blocks pressure-induced FAK and Akt phosphorylation [10].

SIDE EFFECTS

During therapy indicine N-oxide shows hepatotoxicity which was experienced as the asymptomatic elevations of transaminases, hyperbilirubinemia and ascites. The compound was found to be very hepatotoxic when given to a child with acute myelocytic leukemia [30]. In general its toxicity occurs as myelosuppression [37], trombocytopenia [5], nausea and vomiting, anemia, and hepatic dysfunction [17]. The next risk concerning of use indicine-N-oxide in the treatment of cancer is high incidence of veno-occlusive disease related to this therapy [42]. Other sources claim that indicine N-oxide appears to be ineffective in the treatment of osteosarcoma, neuroblastoma, and pediatric brain tumors because higher therapeutic doses are associated with an

unacceptably high incidence of severe, irreversible hepatotoxicity. They even say that the further study of indicine N-oxide in pediatric solid tumors is not recommended [30]. Indicine N-oxide treatment gives partial responses in the mucoepidermoid carcinoma of the salivary glands and with the colon adenocarcinoma [37].

Constipation, and peripheral and central neurotoxicities are the most common side effects during vincristine treatment. What is more, its toxicity is significantly enhanced when combined with azole treatment and can even be life-threatening [38].

Quinine gives many side effects. Those are fortunately not very severe and generally disappear with dose reduction. They mainly include vertigo and tinnitus. Mucositis was significantly more frequently observed in the quinine group. No life-threatening cardiac toxicity was observed [46]. Quinine induced thrombocytopenia in a 64-year-old man who consumed tonic water to relieve nocturnal leg cramps [5]. Quinine does not improve the survival of adult patients with de novo acute myelogenous leukemia, even though it improves the complete remission rate in a small subgroup of patients defined by rhodamine 123 efflux [40]. Quinine caused dizziness [28] and induced a significant increase in the incidence of nausea, vomiting, mucositis and cardiac toxicity. Quinine side effects were observed in 56 of 161 quinine-treated patients and disappeared in all but four cases after one or two 20% dose decreases [41].

Colchicine is a quite toxic agent but in cases of chronic ingestion. The main problem after a colchicine course can be infertility because this drug stops spermatogenesis [10].

CLINICAL TRIALS

In NCI indicine N-oxide was investigated as regards acute lymphocytic leukemia and refractory acute nonlymphocytic leukemia (myelocytic and myelomonocytic). Patients achieved complete or partial remissions in this clinical trial. The drug activity was also investigated in colon and rectum cancer. The drug activity was determined in children with acute lymphoblastic and nonlymphoblastic leukemia, neuroblastoma, brain tumors, Wilm's tumor, rhabdomyosarcoma, Ewing's sarcoma, lymphomas and osteogenic sarcoma. Chemotherapy was evaluated for the advanced or metastatic renal cell cancer [31]. Despite severe side effects the compound is still under examination, as it is sometimes the only hope in cases where other drugs are ineffective.

In NCI vincristine chemotherapy is evaluated in children with low risk acute lymphoblastic leukemia, children with high risk acute lymphoblastic leukemia, in adult acute lymphoblastic leukemia . Combined chemotherapy with vincristine in non-Hodgkin's lymphoma is also assessed. Vincristine was compared in phase III of a randomized study of low dose versus high dose vincristine and combination chemotherapy in pediatric patients with intermediate-risk relapsed B-precursor acute lymphoblastic leukemia. Vincristine is also used in NCI in phase III of a randomized study of ifosfamide, vincristine, and dactinomycin with or without doxorubicin in pediatric patients with non-metastatic rhabdomyosarcoma. The relative safety of a reduced-intensity reintensification regimen comprising dexamethasone, vincristine, cyclophosphamide and anthracyclines vs a standard treatment regimen in pediatric patients with standard-risk acute lymphoblastic leukemia identified by fast clearance of leukemic cells is observed and it looks promising as a new, safer regimen of treatment. Vincristine is used with etoposide, prednisone, and doxorubicin hydrochloride in chemotherapy evaluation in pediatric patients with Hodgkin's lymphoma [31].

NCI also determined the prostate-specific antigen response to continuous low dose oral colchicine. The maximum tolerated dosage of colchicine combined with vincristine/doxorubicin/dexamethasone and plasmapheresis was established in patients with renal failure associated with myeloma. NCI carried out phase I-II pilot chemotherapy with colchicine for refractory Hodgkin's disease, chronic lymphatic leukemia, lung or breast cancer. The maximum dose of colchicine which may be safely administered on a once-a-week basis was determined. In phase I-II chemotherapy with colchicine for refractory chronic lymphocytic leukemia the maximum dose of colchicine was determined, as well as the response rate in patients with chronic lymphocytic leukemia was also determined and the quantitative and qualitative toxicity of colchicine [31].

NCI evaluated efficacy of the drug combination doxorubicin, etoposide, quinidine in the treatment of colorectal cancer and investigated also whether quinidine would reverse multidrug resistance in this type of cancer. It was investigated whether the addition of quinidine elicited a response in patients with colorectal cancer who failed to

respond to doxorubicin. NCI defined the toxicities associated with the combination vinblastine/quinidine in patients with metastatic renal cell carcinoma and determined the maximum tolerated dose of quinidine when used in combination with vinblastine [31].

CONCLUSIONS

These alkaloids are at the stage of clinical studies due to their antitumor efficacy. These drugs possess different mechanisms of action. Some of them, such as caffeine directly affect DNA, others induce apoptosis through different pathways. These compounds have several mechanisms of action, thus have therapeutic potential. Alkaloids are a valuable class of compounds. In addition to antitumor activity may have a preventive measure. These compounds are able to overcome multidrug resistance.

Antitumor activity of plant compounds proves to be a successful research direction. These alkaloids are examples of phytochemicals, which after many stages of research, entered the stage of clinical trials and have a chance to be included in the chemotherapy regimen alone or in combination with other drugs. Described alkaloids are great hope for cancer patients. Particularly for the group of patients with lymphomas, mainly leukemia. Patients with lung cancer and breast cancer also have the chance of new therapies through the research on the anticancer activity of the compounds described.

REFERENCES

1. Arnold E. J., Childress M. O., Fourez L. M., Tan K. M., Stewart J. C., Bonney P. L., Knapp DW. Clinical trial of vinblastine in dogs with transitional cell carcinoma of the urinary bladder. J Vet Intern Med 2011; 25: 1385-90.
2. Barken I., Geller J., Rogosnitzky M. Noscapine inhibits human prostate cancer progression and metastasis in a mouse model. Anticancer Res 2008; 28: 3701-4.
3. Bennis S., Ichas F., Robert J. Differential effects of verapamil and quinine on the reversal of doxorubicin resistance in a human leukemia cell line. Int J Cancer 1995; 28: 283-90.
4. Böll B., Bredenfeld H., Görgen H., Halbsguth T., Eich HT., Soekler M., Markova J. et al. Phase 2 study of PVAG (prednisone, vinblastine, doxorubicin, gemcitabine) in elderly patients with early unfavorable or advanced stage Hodgkin lymphoma. Blood 2011; 118: 6292-8.
5. Brasić J. R. Quinine-induced thrombocytopenia in a 64-year-old man who consumed tonic water to relieve nocturnal leg cramps. Mayo Clin Proc 2001; 76: 863-4.
6. Chougule M. B, Patel A. R., Sachdeva P., Jackson T., Singh M. Anticancer activity of Noscapine, an opioid alkaloid in combination with Cisplatin in human non-small cell lung cancer. Lung Canc 2011; 71: 271-82.
7. Chougule M. B., Patel A., Sachdeva P., Jackson T., Singh M. Enhanced anticancer activity of gemcitabine in combination with noscapine via antiangiogenic and apoptotic pathway against non-small cell lung cancer. PLoS One 2011; 6: e27394.
8. Chougule M. B., Patel A. R., Jackson T., Singh M. Antitumor activity of Noscapine in combination with Doxorubicin in triple negative breast cancer. PLoS One 2011; 15: 6: e17733.
9. Clément M. J., Rathinasamy K., Adjadj E., Toma F., Curmi PA., Panda D. Benomyl and colchicine synergistically inhibit cell proliferation and mitosis: evidence of distinct binding sites for these agents in tubulin. Biochem 2008; 47: 13016-25.
10. Craig D. H., Owen C. R., Conway W. C., Walsh M. F., Downey C., Basson M. D. Colchicine inhibits pressure-induced tumor cell implantation within surgical wounds and enhances tumor-free survival in mice. J Clin Invest 2008; 118: 3170-80.
11. Cyriac S., Rajendranath R., Sridevi V., Sagar TG. Management of high-risk gestational trophoblastic neoplasia with etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine chemotherapy. J Reprod Med 2011; 56: 219-23.
12. Czejka M., Bandak S., Simon D., Schüller J., Weiss C., Schernhammer E. Pharmacokinetic interaction between 4'-epidoxorubicin and the multidrug resistance reverting agent quinine. Z Naturforsch C 1995; 50: 565-70.
13. Dahan A., Sabit H., Amidon GL. Multiple efflux pumps are involved in the transepithelial transport of colchicine: combined effect of p-glycoprotein and multidrug resistance-associated protein 2 leads to decreased intestinal absorption throughout the entire small intestine. Drug Metab Dispos 2009; 37: 2028-36.
14. Genne P., Duchamp O., Solary E., Pinard D., Belon J. P., Dimanche-Boitrel M. T., Chauffert B. Comparative effects of quinine and cinchonine in reversing multidrug resistance on human leukemic cell line K562/ADM. Leukemia 1994; 8: 160-4.
15. Hafeman S. D., Varland D., Dow S. W. Bisphosphonates significantly increase the activity of doxorubicin or vincristine against

canine malignant histiocytosis cells. Vet Comp Oncol. 2012; 10: 44-56.
16. Heidari N., Goliaei B., Moghaddam P. R., Rahbar-Roshandel N., Mahmoudian M. Apoptotic pathway induced by noscapine in human myelogenous leukemic cells. Anticancer Drugs 2007; 18: 1139-47.
17. Hill G. M., Moriarity D. M., Setzer W. N. Attenuation of Cytotoxic Natural Product DNA Intercalating Agents by Caffeine. Sci Pharm 2011; 79: 729-47.
18. Huang H., Lin Z., Lin X., Cai Q., Xia Z., Jiang W. Long-term outcomes of patients with newly diagnosed extranodal natural killer/T-cell lymphoma treated by etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin regimen: a single-institution experience. Leuk Lymphoma 2011; 52: 1041-8.
19. Jackson T., Chougule M. B., Ichite N., Patlolla R. R., Singh M. Antitumor activity of noscapine in human non-small cell lung cancer xenograft model. Cancer Chemother Pharmacol 2008; 63: 117-26.
20. Jhaveri N., Cho H., Torres S., Wang W., Schönthal A. H., Petasis N. A., Louie S. G., Hofman F. M., Chen T. C. Noscapine inhibits tumor growth in TMZ-resistant gliomas. Cancer Lett 2011; 312 :245-52.
21. Jiang M., Zhang H., Jiang Y., Yang Q., Xie L., Liu W., Zhang W., Ji X., Li P., Chen N., Zhao S., Wang F., Zou L. Phase 2 trial of "Sandwich" L-asparaginase, vincristine, and prednisone chemotherapy with radiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma. Cancer 2012; 118: 3294-301.
22. Kaliki S., Shields C. L., Shah S. U., Eagle R. C Jr., Shields J. A., Leahey A. Postenucleation adjuvant chemotherapy with vincristine, etoposide, and carboplatin for the treatment of high-risk retinoblastoma. Arch Ophthalmol 2011; 129: 1422-7.
23. Landen J. W., Hau V., Wang M., Davis T., Ciliax B., Wainer B. H., Van Meir E. G., Glass J. D., Joshi H. C., Archer D. R. Noscapine crosses the blood-brain barrier and inhibits glioblastoma growth. Clin Cancer Res 2004; 10: 5187-201.
24. Lee S. Y., Rhee Y. H., Jeong S. J., Lee H. J., Lee H. J., Jung M. H., Kim S. H., Lee E. O., Ahn K. S., Ahn K. S., Kim S. H. Hydrocinchonine, cinchonine, and quinidine potentiate paclitaxel-induced cytotoxicity and apoptosis via multidrug resistance reversal in MES-SA/DX5 uterine sarcoma cells. Environ Toxicol 2011; 26: 424-31.
25. Letendre L., Ludwig J., Perrault J., Smithson W. A., Kovach J. S. Hepatocellular toxicity during the treatment of refractory acute leukemia with indicine N-oxide. Cancer 1984; 54: 1256-9.
26. Li S., Ghaleb A. M., He J., Bughani U., Bialkowska A. B, Yang V. W., Joshi H. C. Chemoprevention of familial adenomatous polyposis by bromo-noscapine (EM011) in the Apc(Min/+) mouse model. Int J Cancer 2012; 131: 1435-44.
27. Li S., Lei Y., Jia Y., Li N., Wink M., Ma Y. Piperine, a piperidine alkaloid from Piper nigrum re-sensitizes P-gp, MRP1 and BCRP dependent multidrug resistant cancer cells. Phytomedicine 2011; 19: 83-7.
28. Marguerite V., Beri-Dexheimer M., Ortiou S., Guéant JL., Merten M. Cobalamin potentiates vinblastine cytotoxicity through downregulation of mdr-1 gene expression in HepG2 cells. Cell Physiol Biochem 2007; 20: 967-76.
29. Miller T. P., Chase E. M., Dorr R., Dalton W. S., Lam K. S., Salmon S. E. A phase I/II trial of paclitaxel for non-Hodgkin's lymphoma followed by paclitaxel plus quinine in drug-resistant disease. Anticancer Drugs 1998; 9: 135-40.
30. Miser J. S., Smithson W. A., Krivit W., Hughes C., Davis D., Krailo M., Hammond D. Phase II trial of indicine N-oxide in relapsed pediatric solid tumors. Invest New Drugs 1991; 9: 339-42.
31. Morjani H., Belhoussine R., Lahlil R., Manfait M. Pirarubicin nuclear uptake does not correlate with its induced cell death effect during reversal of multidrug resistance by quinine in human K562 and CEM leukemic cells. Eur J Haematol 1998; 61: 240-9.
32. National Cancer Institute [online]. Bethesda, United States: [access: 23 Feb. 2012]. Available on the Internet: cancer.gov
33. Newcomb E. W., Lukyanov Y., Alonso-Basanta M., Esencay M., Smirnova I., Schnee T., Shao Y., Devitt M. L., Zagzag D., McBride W., Formenti S. C. Antiangiogenic effects of noscapine enhance radioresponse for GL261 tumors. Int J Radiat Oncol Biol Phys 2009; 74: 655-6.
34. Newcomb E. W., Lukyanov Y., Schnee T., Ali M. A., Lan L., Zagzag D. Noscapine inhibits hypoxia-mediated HIF-1alpha expression andangiogenesis in vitro: a novel function for an old drug. Int J Oncol 2006; 28: 1121-30.
35. Newcomb E. W., Lukyanov Y., Smirnova I., Schnee T., Zagzag D. Noscapine induces apoptosis in human glioma cells by an apoptosis-inducing factor-dependent pathway. Anticancer Drugs 2008; 19: 553-63.
36. Olsen I. H., Langer S. W., Jepsen I., Assens M., Federspiel B., Hasselby J. P., Hansen C. P., Kjaer A., Knigge U. First-line treatment of patients with disseminated poorly differentiated neuroendocrine carcinomas with carboplatin, etoposide, and vincristine: a single institution experience. Acta Oncol 2012; 51: 97-100.

37. Rathinasamy K., Jindal B., Asthana J., Singh P. Griseofulvin stabilizes microtubule dynamics, activates p53 and inhibits the proliferation of MCF-7 cells synergistically with vinblastine. BMC Cancer 2010; 10: 213.
38. Rendine S., Pieraccini S., Sironi M. Vinblastine perturbation of tubulin protofilament structure: a computational insight. Phys Chem Chem Phys 2010; 12: 15530-6.
39. Schie R. M., Brüggemann R. J., Hoogerbrugge P. M., te Loo D. M. Effect of azole antifungal therapy on vincristine toxicity in childhood acute lymphoblastic leukaemia. J Antimicrob Chemother 2011; 66: 1853-6.
40. Solary E., Witz B., Caillot D., Moreau P., Desablens B., Cahn J. Y., Sadoun A. Combination of quinine as a potential reversing agent with mitoxantrone and cytarabine for the treatment of acute leukemias: a randomized multicenter study. Blood 1996; 88: 1198-205.
41. Su W., Huang L., Ao Q., Zhang Q., Tian X., Fang Y., Lu Y. Noscapine sensitizes chemoresistant ovarian cancer cells to cisplatin through inhibition of HIF-1α. Cancer Lett 2011; 305: 94-9.
42. Sugiura H., Kawabata H., Ichikawa T., Koarai A., Yanagisawa S., Kikuchi T., Minakata Y., Matsunaga K., Nakanishi M., Hirano T., Akamatsu K., Furukawa K., Ichinose M. Inhibitory effects of theophylline on the peroxynitrite-augmented release of matrix metalloproteinases by lung fibroblasts. Am J Physiol Lung Cell Mol Physiol 2012; 302: 764-74.
43. Sung B., Ahn K. S., Aggarwal B. B. Noscapine, a benzylisoquinoline alkaloid, sensitizes leukemic cells to chemotherapeutic agents and cytokines by modulating the NF-kappaB signaling pathway. Cancer Res 2010; 70: 3259-68.
44. Taylor C. W., Dalton W. S., Mosley K., Dorr R. T., Salmon S. E. Combination chemotherapy with cyclophosphamide, vincristine, adriamycin, and dexamethasone (CVAD) plus oral quinine and verapamil in patients with advanced breast cancer. Breast Cancer Res Treat 1997; 42: 7-14.
45. Turaka K., Shields C. L., Meadows A. T., Leahey A. Second malignant neoplasms following chemoreduction with carboplatin, etoposide, and vincristine in 245 patients with intraocular retinoblastoma. Pediatr Blood Cancer 2012; 59: 121-5.
46. Wang Y. N., Shuai P. Q., Guo Y. J., Zhang L. S. Analysis of loss of heterozygosity induced by vinblastine at tk locus in human lymphoblastoid cell line TK6. Sichuan Da Xue Xue Bao Yi Xue Ban 2006; 37: 558-61.
47. Wattel E., Solary E., Hecquet B., Caillot D., Ifrah N., Brion A., Milpied N. et al. Quinine improves results of intensive chemotherapy (IC) in myelodysplastic syndromes (MDS) expressing P-glycoprotein (PGP). Adv Exp Med Biol 1999; 457: 35-46.
48. Wigler P. W., Lyon K. L., Patterson F. K., La Loggia A. J., Diaz-Araúzo H., Reddy M. S., Cook J. M. Epoxide metabolite of quinine and inhibition of the multidrug resistance pump in human leukemic lymphoblasts. Mol Pharmacol 1994; 46: 562-7.
49. Yoshida K., Nagai T., Ohmine K., Uesawa M., Sripayap P., Ishida Y., Ozawa K. Vincristine potentiates the anti-proliferative effect of an aurora kinase inhibitor, VE-465, in myeloid leukemia cells. Biochem Pharmacol 2011; 82: 1884-90.
50. Yunos N. M., Beale P., Yu J. Q., Strain D., Huq F. Studies on combinations of platinum with paclitaxel and colchicine in ovarian cancer cell lines. Anticancer Res 2010; 30: 4025-37.
51. Zhong Y. J., Shi F., Zheng X. L., Wang Q., Yang L., Sun H., He F., Zhang L., Lin Y., Qin Y., Liao L. C., Wang X. Crocetin induces cytotoxicity and enhances vincristine-induced cancer cell death via p53-dependent and -independent mechanisms. Acta Pharmacol Sin 2011; 32: 1529-36.
52. Zhou Q., Lui V. W., Lau C. P., Cheng S. H., Ng M. H., Cai Y., Chan S. L., Yeo W. Sustained antitumor activity by co-targeting mTOR and the microtubule with temsirolimus/vinblastine combination in hepatocellular carcinoma. Biochem Pharmacol.2012; 83: 1146-58.

Acknowledgement: This study was supported in part by Polish Ministry of Sciences and Higher Education, grant No: NN 405162639.