USEFULNESS OF ALKALOIDS IN TREATMENT OF CANCER. PART 1: A REVIEW

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S u m m a r y. Based on PUBMED and the National Cancer Institute at the National Health Institute in the United States database authors have done a review concerning anticancer activity of alkaloids: indicine N-oxide, Noscapine, Vinblastine, Vincristine, Colchicine, Quinine and Quinidine. Data from the National Cancer Institute provide information about the stage of investigations and what can be expected to know about the examined compound in the nearest future. The article is divided into two parts: first of them concerns mechanisms of anticancer activity of mentioned compounds, while the second is composed of chapters concerning the use of these alkaloids in the anticancer therapy, their sensitizing, antimetastatic and chemoprotective activity; side effects and running clinical trials on patients with different types of cancer. Described alkaloids show a number of different pharmacological effects but they are the most promising as regards treatment of cancer. They have a direct effect on a number of tumor cell lines, as well as have evidenced activity in patients with various cancer types. Antitumor activity of alkaloids relays on inhibiting proliferation by affecting cell division or inducing apoptosis in cancer cells. These mechanisms are very sophisticated. Some of them directly affect DNA, others induce apoptosis through different pathways. These compounds are also able to overcome multidrug resistance. Described alkaloids are active, inter alia, in relation to the leukaemic cells, lung, breast, brain, prostate and ovarian cancer.
K e y   w o r d s: alkaloids, indicine N-oxide, noscapine, vinblastine, vincristine, colchicine, quinine, quinidine, cancer

INTRODUCTION

Phytochemical compounds have long been known from their therapeutic activity. Available in nature, they are among the most pharmacologically active chemicals used in medicine. They should not be neglected any more as they are as powerful as synthetic drugs. The aim of this paper was collection of information about anticancer activity of alkaloids. Alkaloids are plant metabolites known since 1813, the first alkaloid known was morphine. This compounds are in general chemically heterocyclic. They contain an atom of nitrogen in their chemical structure and possess alkaline character. Alkaloids are naturally biosynthesized from amino acids and occur in various parts of plants thus giving them pharmacological properties, depending on the team of alkaloids occurring. These compounds are the most common reason for poisonous properties of plants, as well as they make some raws a strong antidote. Chemical structure of morphine was explained in 1952 and today we are able to know the chemical structure of all known alkaloids [27]. They are divided in to classes depending on the structure of the ring. In general, the properties of described compounds are also known and they are effective in many various diseases. However, nowadays, their anticancer properties attract a great deal of interest. Although part of this group of compounds , such as colchicine, vincristine or vinblastine, has been used in treatment of cancer for years, these compounds are still in the phase of clinical trials in order to find new properties. Others are the newest revelations as regards their antineoplastic or supportive activity in cases of cancer. Many of alkaloid derivatives are in clinical usage and alkaloids are the basis for continuous creation of new drugs.

METHODS

PUBMED and the National Cancer Institute at the National Health Institute in the United States databases were searched using the following terms:

alkaloids; indicine N-oxide; Noscapine; Vinblastine; Vincristine; Colchicine; Quinine; Quinidine. More than 300 English language abstracts were analyzed and the full texts of selected articles were obtained. Reference lists of review articles and relevant trials were searched in February 2012. Data from the National Cancer Institute provide information about the stage of investigations and what can be expected to know about the examined compound in the nearest future. In this part of article authors are introducing the mechanisms of anticancer activity of mentioned compounds.

INDICINE N-OXIDE

Research of this compound started because of Heliotropium indicum Linn. (Boraginaceae) extracts of widely used herbs in Ayurvedic medicine. These extracts showed significant activity in several experimental tumor systems. The active principle was isolated and shown to be the N-oxide of the pyrrolizidine alkaloid- indicine, previously isolated from this plant [19]. It has been proved that indicine N-oxide has antimitotic properties and can cause chromosomal damage [28]. It is more active than its free base indicine [29]. Nonetheless the compound is still poorly known and there are few data about its activity and mechanism of action.

NOSCAPINE

Noscapine is an isoqiunoline alkaloid found in opium latex. As opium latex was the first known source of alkaloids, noscapine was revealed relatively early, four years after morphine, in 1817. It provides approximately 10% of opium alkaloids [22]. Unlike most other alkaloids obtained from opium latex, noscapine is not sedative but has been used as an antitussive drug in various countries. Recently, it has been introduced as an antimitotic agent which acts used orally. Noscapine seems to be a very promising drug as it is effective when the resistance to other anticancer drugs, such as paclitaxel, occurs. Therefore, this alkaloid and its analogs have great potential to be novel anticancer agents [25]. What is unbelievably favorable about side effects of the noscapine therapy is that it has been proved to be nontoxic. However, there is a problem about pharmacokinetics of noscapine. Significant elimination of the disease is hard to be achieved, since the bioavailability of noscapine to tumors appears only at an oral dose of 300 mg/kg body weight [25].

VINBLASTINE & VINCRISTINE

Vinblastine and Vincristine are natural alkaloids, indole derivatives isolated from the plant Vinca rosea Linn. (Apocynaceae) [27]. Vinblastine isolated in 1958 by Noble and comp. is one of the first anticancer drugs used in history. Both are used as a sulfate salt infusion[32] and have similar mechanisms of action but the drugs are used in different disease entities. Both agents give severe side effects, nonetheless they are old and well known drugs. A method of transforming vinblastine to vincristine has been developed, and it is possible to synthesize both of them [32].

COLCHICINE

Colchicine is an alkaloid from group of protoalkaloids, isolated from Colchicum autumnale (Liliaceae) with anti-gout and anti-inflammatory activities. It is also used in cases of chondrocalcinosis and familial Mediterranean fever (FMF) and pericarditis. The exact mechanism of action by which colchicine exerts its effect has not been completely established. It is known that it binds to tubulin, thereby interfering with the polymerization of tubulin, interrupting microtubule dynamics, and disrupting mitosis. This leads to an inhibition of migration of leukocytes and other inflammatory cells, thereby reducing the inflammatory response to deposited urate crystals. Colchicine may also interrupt the cycle of monosodium urate crystal deposition in joint tissues, thereby also preventing the resultant inflammatory response. Overall, colchicine decreases leukocyte migration and phagocytosis to inflamed areas, and inhibits the formation and release of a chemotactic glycoprotein that is produced during phagocytosis of urate crystals [27]. Because of these mechanisms of action colchicine started to be examined as regards its anticancer activity. It is a relatively old chemotherapeutic but it is still under examination in this subject. What is more, this alkaloid is found to be helpful in some problems accompanying the process of chemotherapy. For example, daily washings with colchicine solution improve mucositis in patients with hematological malignancies undergoing chemotherapy [7].

QUININE

Quinine is a quinoline alkaloid isolated from the bark of the Cinchona tree (Rubiaceae) [27]

used as Cininum hydrochloridum and Chininum sulfuricum [8]. It was an antimalarial remedy, which was life-saving, in times when there was no other remedy for malary. Nowadays this bitter drug replaced by new, safer drugs is popular mostly because of its use in tonics production. Nonetheless it possesses anti-fever, anti-inflammatory and pain killing activity. Quinine may be a useful test to detect inhibition of liver CYP3A4 activity. Further studies are needed to determine whether it can provide a quantitative measure of CYP3A4 activity suitable for inter-subject comparison [41].

QUINIDINE

Quinidine is a quinoline alkaloid extracted from the bark of the Cinchona tree (Rubiaceae), which is the oldest antiarrhythmic drug with class 1A antiarrhythmic effects. It stabilizes the neuronal membrane by binding to and inhibiting voltage-gated sodium channels, thereby inhibiting the sodium influx required for the initiation and conduction of impulses resulting in an increase in the threshold for excitation and decreased depolarization during phase 0 of the action potential [27]. In addition, the effective refractory period, action potential duration, and effective refractory period/ action potential duration ratios are increased, resulting in decreased conduction velocity of nerve impulses. The drug is a known inhibitor of cytochrome P450-mediated nifedipine metabolism [17]. Quinidine is a not specific CYP2D6 inhibitor so it influences metabolism of many xenobiotics [10].

It was shown that nifedipine and quinidine bind to different P450 3A4 species, with distinct conformations. Quinidine acted as an allosteric inhibitor by switching nifedipine binding from nifedipine-metabolizing species I to the nonmetabolizing species II [17]. It possesses antimalarial effects but it is weaker than those of quinine. Quinidine exerts its antimalarial activity by acting primarily as an intra-erythrocytic schizonticide through association with the heme polymer (hemazoin) in the acidic food vacuole of the parasite thereby preventing further polymerization by heme polymerase enzyme. This results in accumulation of toxic heme and death of the parasite [27].

Both quinine and quinidine do not seem to be effective themselves as regards cancer treatment. However, they are very promising in cases of multidrug resistance. They attract a lot of attention because of their effects on resistant cell lines, especially quinine raises high hopes.

MECHANISM OF ANTICANCER ACTIVITY INDOCINE N-OXIDE

Indicine N-oxide is an antineoplastic drug which can alkylate and crosslink DNA [NCI 2012]. Although many tests have been carried out to find the target of its anticancer activity, the mechanism of its action is not known precisely. It has been proved that the compound is effective in the murine P388 leukemia model [28].

In nude mice bearing human cancer xenografts of hematopoietic, breast, lung, ovarian, brain and prostate origin it has been revealed that the alkaloid binds to tubulin and alters its conformation, resulting in a disruption of the dynamics of microtubule assembly. Thus it inhibits mitosis and results in cell death [11, 12, 23, 27].

It has been revealed that noscapine can reverse G(2)/M arrest in wild type murine embryonic fibroblasts and cause both β-catenin levels and activity to fall o half the original levels with a concomitant reduction in cell proliferation-inducing cyclin D1, c-Myc, and induction of cytostatic protein p21 before caspase-3 activation in these cells [5]. What is very interesting is that noscapine suppresses phosphorylation and nuclear translocation of p65, leading to inhibition of NF-kB reporter activity induced by various components of the NF-kB activation pathway. Also the activity of the NF-kB-containing cyclooxygenase-2 promoter is inhibited by noscapine. The induction of apoptosis by up regulation of Bax and Cytochrome c (Cyt-c) protein and downregulation of Bcl-2 protein by noscapine has been proved in gastric cancer cell lines. In this case caspase-3 and caspase-9 were activated [31, 38]. In human glioma cell lines noscapine apoptosis was associated with activation of the c-jun N-terminal kinase signaling pathway concomitant with inactivation of the extracellular signal regulated kinase signaling pathway and phosphorylation of the antiapoptotic protein Bcl-2. Noscapine-induced apoptosis was associated with the release of mitochondrial proteins and cytochrome c [23].

Noscapine - dependent suppression of tumor growth involved up regulation of PARP, Bax, caspase-3 and repression of Bcl-2 expression. An increase in Bax/Bcl-2 ratio suggested involvement of a mitochondrial mediated apoptotic process. An increase in Bax/Bcl-2 ratio with noscapine was observed in a significant dose-dependent manner [5]. In myeloid leukemia cells noscapine increased the activity of caspase -2, -3, -6, -8 and -9, poly(ADP

ribose) polymerase cleavage. Phosphatidylserine on the outer layer of the cell membrane, nucleation of chromatin, and DNA fragmentation were detected after noscapine stimulation. No inhibitory effect of the caspase-8 inhibitor on caspase-9 activity was observed [38]. In colorectal carcinoma 20cells it was shown that p21 has a proapoptotic role in noscapine treatment and p53 is a necessary but not sufficient condition for noscapine-mediated apoptosis [1].

VINBLSTINE

Vinblastine binds to tubulin and inhibits microtubule formation, resulting in disruption of mitotic spindle assembly and arrest of tumor cells in the M phase of the cell cycle. This agent may also interfere with amino acid, cyclic AMP and glutathione metabolism. It influences on calmodulin-dependent Ca++ -transport ATPase activity and cellular respiration Nucleic acid and lipid biosynthesis is also the target of vinblastine action [27]. Vinblastine, wedging between tubulin heterodimers, mediates part of the interactions between them and acts by crosslinking the two proteins, leading to the curved polymers rather than to their disassembly [32, 43]. It weakly activated human full-length NR1I2, but had no influence on NR1I3. This compound is able to induce CYP3A4 via 26 mechanism and can cause interactions with other CYP3A4 substrates [35]. Vinblastine induced arrest of MOLT-4 cells at the M phase [45]. It increased the affinity of stathmin for tubulin [6]. The binding site of vinblastine is largely unknown, but it was reported that vinblastine and the amino-terminal part of RB3 protein stathmin-like domain binding sites share a hydrophobic groove on the alpha-tubulin surface [9]. This compound inhibits palmitoylation of tubulin in vivo in CEM cells. In addition, microtubules were disassembled and cells became apoptotic [2].

VINCRISTINE

Vincristine demonstrates antimitotic and antineoplastic activities. It binds irreversibly to microtubules and spindle proteins in the S phase of the cell cycle and interferes with the formation of the mitotic spindle, thereby arresting tumor cells in the metaphase. This agent depolymerizes microtubules and may also interfere with amino acid, cyclic AMP and glutathione metabolism, calmodulin-dependent Ca++ -transport ATPase activity, cellular respiration

and nucleic acid and lipid biosynthesis [27]. In resistant cells vincristine- induced apoptosis was observed, coupled with decreasing expression of the protein XIAP. HMGB1-mediated up regulation of Mcl-1 transcription was confirmed to be an important mechanism by which autophagy protects gastric cancer cells from apoptosis induced by vincristine [44]. A high dose of vincristine induces a concomitant overexpression of 32 and survivin, which was associated with a low apoptotic index in the K562 –chronic myeloid leukemia cell line [13, 14, 18, 36]. Vincristine triggered apoptosis and cell cycle delay at the G(2)/M phase and also up-regulated p16 [15, 34]. It was found that vincristine induces AMP-activated protein kinase activation (AMP-activated protein kinase α, Thr 172) and Acetyl-CoA carboxylase (ACC, Ser 79) (a downstream molecular target of AMP-activated protein kinase) phosphorylation in cultured B16 melanoma cells [4]. Good efficacy of intralesional vincristine for treating nodular lesions in classic Kaposi's sarcoma was reported. It may be effective in recalcitrant verrucas [20, 21].

The **colchicine** – induced loss of mitochondrial membrane potential, activation of caspase-3 and 9, upregulation of Bax and downregulation of Bcl-2 show evidence for the colchicine activity on apoptosis, at least, by acting via the intrinsic apoptotic pathway [3]. Colchicine inhibits both tubulin polymerisation as well as depolymerisation [16].

Quinine possesses many mechanisms of action, including reduction of oxygen intake and carbohydrate metabolism, disruption of DNA replication and transcription via DNA intercalation. It can reduce the excitability of muscle fibers via alteration of calcium distribution [26, 30].

Quinidine regulates growth and differentiation in human breast tumor cells, but the immortalized mammary epithelial MCF-10A cell line is insensitive to quinidine. It was supposed that suppression of c-myc gene expression is involved in the preferential growth and differentiation response of breast tumor cells to quinidine. Quinidine decreases c-myc promoter activity in MCF-7 cells [24]. Treatment with quinidine reduces proliferation of neurofibromatosis type 2-NF2 Schwann cells in a concentration dependent manner but did not reduce proliferation of normal Schwann cells [33]. It was investigated in C6 glioma cells that the antiproliferative effect of quinidine is not due to a simple membrane depolarization but is caused by a block of ornithine

decarboxylase activity [42]. Quinidine selectively reduced the proliferation of merlin-deficient HMM cell lines by causing a G(0)/G(1) arrest, whereas the proliferation rates of merlin-expressing HMM cell lines remains unchanged. The effect of quinidine on the proliferation of HMM cell lines appeared to be correlated with the NF2 gene status but not with the K(+) outward current. No relation to cytochrome P450 2D6 mutations was detected [37, 39, 40].

CONCLUSIONS

Described alkaloids are a very interesting group of plant compounds. They show a number of different pharmacological effects. They are also very promising class of compounds for the treatment of cancer. Alkaloids have a direct effect on a number of tumor cell lines, as well as have evidenced activity in patients with various cancer types. Antitumor activity of alkaloids relays on inhibiting proliferation by affecting cell division or inducing apoptosis in cancer cells. These mechanisms are very sophisticated. The alkaloids are active, inter alia, in relation to the leukaemic cells, lung, breast, brain, prostate and ovarian cancer.

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