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Noscapine as Anticancer Agent & Its Role in Ovarian Cancer

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Abstract

Cancer is a public health problem accounting for an estimated 9.6 million deaths worldwide, according to the latest WHO report, mainly affecting low-middle income countries. Noscapine (narcotize), a non-toxic benzylisoquinoline alkaloid derived from opium poppy, is commonly used as a cough suppressant in humans and exhibited various activities against a variety of cancers with unclear mechanism of action. Unlike other alkaloids obtained from opium poppy, noscapine is not sleep-inducing, hypnotic drug, rendering it as non-addictive drug and therefore used as antimitotic & antitussive drug around the world, can be orally consumed. Ovarian Cancer is one of the common causes of gynecologic cancer affecting women around the world. The main reason for treatment failure and mortality is the drug resistance against DDP (cisplatin), which has emerged the use of Noscapine against drug-resistant ovarian cancer cell line SKOV3/DDP by activation of apoptosis. Herein, we will describe noscapine chemically; its medicinal utility and pharmacological history behind the noscapine family of compounds then follow its journey for treating ovarian cancer (Figure 1).

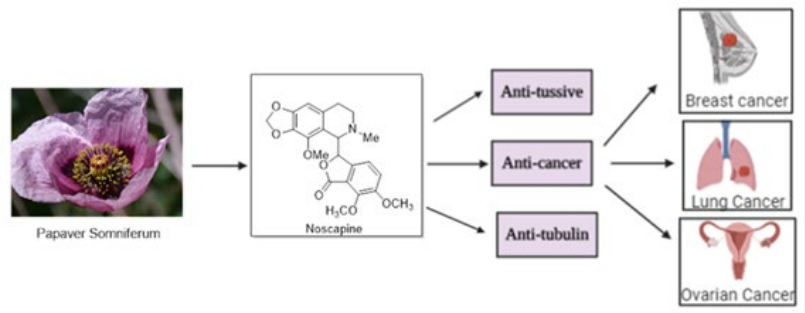

Figure 1: The compounds-2 and 3 2-amino-6-(9,10-dihydro-9-oxoacridin-2-yl)-4-aryl-pyridine-3-carbonitriles.

Keywords: Noscapine; Mitosis; Apoptosis Antitussive; Metastasis; Sipuleucel-T vaccine

Introduction

Cancer remains the second frightful disease after cardiovascular diseases causing millions of deaths worldwide. Cancer accounts for an estimated 10 million deaths globally in 2018, especially in low and middle-income countries according to the recent WHO report [1,2]. Both external factors, i.e. regular usage of tobacco products, alcohol, and unhealthy food & internal factors that include genetic mutation in genetic material of cells, hormonal disorders involve the major risk factor for cancer and accounted for approximately 20% cancer deaths [3,4]. It is characterized by uncontrolled cell proliferation of normal cells that divide uncontrol-

lably, and an absence of cell death causes an abnormal cell clump, which we called tumors that grow and metastasize to other parts of the body and finally leads to death [5]. Several types of cancer are reported in human beings; among them breast cancer is top listed in females followed by lung cancer in males [6,7].

The main systemic treatment options currently used for metastatic cancers are chemotherapy, hormone therapy, immunotherapy, cancer vaccination, and biological therapies, while surgery & radiotherapy are primary treatment used for non-metastatic cancers [8]. These frontline treatments depend upon type of cancer, its stage, and location which are often accompanied by harsh side effects involving toxicity, limited bioavailability, quick clearance and restricted metastasis [9]. Chemotherapeutic agents involve drugs that could show promising results either alone or in combination with other cancer therapies [10].

These agents include topoisomerase inhibitors, doxorubicin, carboplatin, cisplatin, docetaxel and paclitaxel etc. [11], are highly efficient but these agents also have limitations like cost, side effects, and toxic. Classical drugs targeted directly DNA of the cell which proved ineffective, while contemporary drugs involve targeting at protein that possessed abnormal expression inside the cell, which was successful in certain malignancies [12]. It also often limited by cancer cell's resistance to these drugs as they go through mutations and side effects on normal tissues and cells with fast proliferation rates, such as bone marrow, hair follicles.

Recently, new FDA approved targeted therapies involve blocking of specific cancer protein to cause cancer cell death due to apoptosis, specific delivery to cancer drugs to cancer cells, blocking of transduction pathways, thereof minimizing side effects [13]. Several vaccines have been approved by FDA for the treatment of cancer, including hepatitis B vaccine and human papillomavirus (HPV), lately Sipuleucel-T (Provenge) has been approved by FDA in U.S. to treat prostate cancer which can no longer be treated by hormone therapy [14]. The use of various types of nanoparticles (NPs) has gained attraction recently in delivering anticancer drugs. Nanocarriers increase the therapeutic efficacy of drugs inside the tumor cell; also, they improve their specificity [15].

Lately, the emphasis on natural products was done in search of a novel treatment of this deadly disease cancer. Moreover, the cytotoxic effects of a few members of Papaveraceae family have been considered in medicines made in India, China & Iran to cure chronic cough, diarrhea, and gastrointestinal problems [16]. Noscapine (Narcotine), discovered in 1817, a phthalide isoquinoline alkaloid is a natural product derived from the opium poppy, Papaver somniferum. Unlike other alkaloids obtained from opium, noscapine is not sedative, non-narcotic, and non-analgesic. Noscapine is initially marketed as a safe; antitussive (cough suppressant) agent in early 1960's and had a low toxic profile [17]. Later it was found to possess anticancer activity due to its action on tubulin; it binds with tubulin and slows down tumor growth [18]. In past years, many potential anticancer drug targets have been identified for its effective treatment. The current review describes Noscapine and its analogs as promising anticancer targets.

Noscapine, a Biologically Active Natural Product

Noscapine is a widely used antitussive medication and now used as promising anticancer medicine, which can be administered orally. Noscapine has been found to inhibit progression of breast cancer, ovarian cancer, lung cancer, and prostate cancer, both in vitro & in vivo with no toxicity to other parts of human body such as heart, kidney, liver, bone marrow [19]. Based on literature, we observed that Noscapine has chemical similarity with colchicine, and hence it binds in a similar way to tubulin that leads to change in conformation affecting microtubule assembly and finally arrests mitosis.

Noscapine can also be used in combination with other anti-tumor drugs; for example, its combination with doxorubicin, an anthracycline drug against triple-negative breast cancer. They demonstrated that Noscapine inhibited growth of MDA-MB-231 (IC50=36 mM) and MDA-MB-468 (IC50=42 mM) cells with Confidence Interval (CI) values (0.59) that suggest strong synergistic interaction of Noscapine and Doxorubicin with increase in apoptotic cells significantly [20]. Similarly, Noscapine combination with gemcitabine is used in the treatment of non-small lung cancer [21]. Noscapine is water-soluble; it readily crosses the blood-brain barrier. Also, its oral administration property potentiates the anti-cancer activity of doxorubicin as well as gemcitabine in a synergistic manner through anti-angiogenic apoptotic pathways.

In 2016, Isobolographic method has been utilized to decipher the interaction between Noscapine and Cisplatin against A549 and H460 lung cancer cells in vitro and also in vivo in murine xenograft model. The results demonstrated synergistic effect of Noscapine and Cisplatin together with reduced tumor volume by 78% as compared with 38% by Cisplatin or 35% by Noscapine alone in murine xenograft lung cancer model [22]. The mechanistic interaction of Noscapine and Lysozyme has been recently studied by Damini [23]. The study investigated their conformational changes and helped in understanding biophysical properties on interaction of Lysozyme with Noscapine.

Noscapine Analogs as Promising Anticancer Agents

Over the past years, many analogs of Noscapine have been synthesized and tested for anti-cancer activity, which is found superior to the parent Noscapine. These derivatives were chemically synthesized by modifying the parent Noscapine, whereas keeping the parent scaffold intact [24]. There are three generations of noscapinoids; first-generation noscapinoids were chemically synthesized by modifying isoquinoline and benzofuranone rings of Noscapine [25]. This also includes 9-halogenated (chloro, bromo, iodo-noscapine), 9-amino, 9-nitro, and 9-azido analogs.

9-bromonoscapine was found to have higher tubulin binding activity than Noscapine with improved effect on tubulin polymerization. Besides 9-bromonoscapine, in vitro cytotoxicity on U-87

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human glioblastoma cell lines by MTT assay were evaluated for 9-chloro, 9-iodonoscapine [26]. At 50 μM concentration, 9-bromo, 9-chloro, 9-iodonoscapine killed 51%, 88%, and 57% cells respectively after 72h, whereas Noscapine killed only 40% of the cell. The results reveal 9-chloonoscapine as more potent anticancer agent than Noscapine and 9-Bromonoscapine. However, at 1 μM concentration, both 9-chloro and 9-bromo derivatives showed similar activity results (Figure 2).

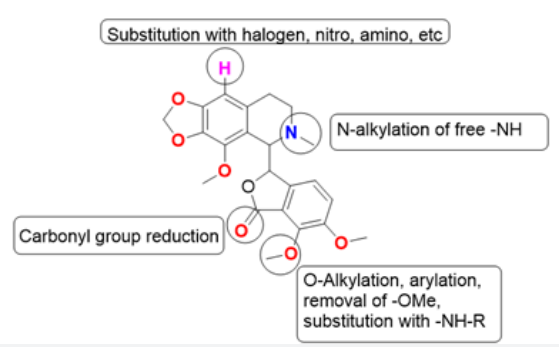

Figure 2: Analogues of Noscapine.

9-nitro-nos proved useful in mainly those cells that show multidrug resistance, for ex- lymphoma and an ovarian cancer cell. Computational studies showed that 9′-aminonoscapine analog would bind to tubulin at the site, which overlapped with the colchicine-binding site and could possess improved antitumor activity when compared to Noscapine. Amino noscapine effectively reduced the intrinsic fluorescence of tubulin in comparison to Noscapine. In halogenated noscapinoid, chlorinated derivative shows good results against ovarian cancer cells. Second generation noscapinoids represent the O-alkylated and O-acylated by modifying benzofuranone ring of Noscapine.

The 7-acetyl derivative of Noscapine was prepared to analyze the influence of the polarizable carbonyl group on activity in contrast to the inert 7-OMe of parent compound noscapine. 7-substituted Noscapine analog with acetyl group showed better activity as compared to Noscapine in A549, MCF7, PC3 cell lines [27]. Third generation noscapinoids were produced by alteration in substituents coupled to the nitrogen of the isoquinoline ring. The substitution of the N-methyl group with longer alkyl chain derivative was seemed to be less stable. All these derivatives are more potent in inhibiting the proliferation of Human Cancer cells [28].

Noscapine Mechanism of Action

Although the molecular mechanism of anticancer activity of Noscapine is not yet clear, however, several experiments indicate that Noscapine induces apoptosis tumor cells. The induction of apoptosis is verified by the increase in activity of caspase -2, -3, -6, -8 and -9, nucleation of chromatin, DNA fragmentation, and detection of phosphatidyl serine on the outer layer of the cell membrane. Hence this could be used as treatment of hematological malignancies [29]. Newcomb [30] have done a similar study on human glioma cells and demonstrated that Noscapine is an inhibitor of the Hypoxia-inducible factor-1 (HIF-1) pathways in human glioma cell lines and umbilical vein endothelial cells. Also, Noscapine activates JNK signaling pathway, inactivate ERK signaling pathway and phosphorylation of the Bcl-2, an antiapoptotic protein while inducing apoptosis. In glioma cell lines, sometimes there is the release of mitochondrial protein AIF along with PARP and cytochrome C cleavage. While in others, AIF released without PARP and cytochrome C cleavage.

Noscapine molecular mechanism of action on tubulin reveals that it binds to tubulin. The evidence revealed by concentration-dependent quenching of the tryptophan fluorescence of tubulin [18]. Also, in the literature survey, it is found that Noscapine has altered the dynamic instability of microtubules by increasing the attenuated state [31], in this way it arrests the cancer cells. Noscapine reduces the catastrophic frequency and increases the rescue frequency. Therefore, Noscapine suppresses the overall dynamicity of microtubule by 60%. The binding sites of Noscapine and its derivative have been investigated in silico [32] Findings predict that the binding site may lie at the a/b-tubulin interface near the colchicine's binding site.

For the verification, Fluorescence experiment was performed, and the results were interpreted that Noscapine has no interference with binding sites of Colchicine. Alisaraie et al. [33] used molecular docking and molecular dynamic (MD) simulations to study the binding site of Noscapine in silico. The result indicated that the binding sites of Noscapine were found at the intradomain region of the a- and b-tubulin. The same studies were performed on nitrated and brominated Noscapine, and they experimentally measured the dissociation constants proved them a better option [34]. The result could have been improved by studying the noscapine binding to tubulin in a dynamic mode and by including water molecules.

There are two GTP-binding sites; one is an exchangeable site (E-site), and other is nonexchangeable site (N-site) in the -and b-tubulin subunits. GTP molecule was added to the system in the N and E-site. In the a-tubulin subunit, the water molecule surrounding the binding sites hold the Noscapine and forced it toward the

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central region of the intradomain interface. The dynamic nature of the surrounding environment of Noscapine and the above event were found to force it toward GTP at the N-site, as the distance between the centers of mass of GTP and Noscapine decreased around 20 ns of the MD simulations. Distance variation between the center of mass of GTP and the important elements of the N-site effect the structure element of tubulin [35]. The binding of Noscapine revealed that the stability of tubulin elements of the E-site components has increased considerably and the dynamical motions of parts of tubulin have reduced. These elements interfere with the noscapine longitudinal interaction with microtubule, and as a result, positive effects on microtubule polymerization observed.

Noscapine activity as an anticancer agent is mediated by inhibiting NF-kB activation pathway. It also abrogated all the inducible expression of proteins, which are regulated by transcription factors NF-kB, including angiogenesis, survival, proliferation, and invasion. It suppresses the proliferation of human leukemia and myeloma cells by suppressing the NF-Kb signaling pathway. For the inhibition of activity of NF-kB reporter, it must suppress phosphorylation and nuclear translocation of p65; that also inhibited the activity of the NF-Kb-containing cyclooxygenase-2-promoter. One of the important mechanisms of anticancer agents involves antiangiogenic activity; hence, Noscapine also possesses antiangiogenic activity. There are two mechanisms of action involved by which it could show antiangiogenic activity. Firstly, by decreasing HIF-1 expression in hypoxic tumor cells and upregulating the target genes like VEGF [36].

While in others, it inhibits the endothelial cells from forming blood vessels in response to VEGF stimulation. Noscapine being a low toxic agent acted well as an anticancer agent in several animal models of cancer and inhibited the HIF-1 pathway. Considering these properties, it should be considered as antiangiogenic chemotherapeutic agent for glioma [37].

Biological Aspects of Noscapine

Antitussive Activity

Since the 1960s, Noscapine has been widely used as antitussive (cough-suppressing effect) throughout the world with high safety. Noscapine is a drug with a low-toxicity profile, and hence it is orally administered drug either in tablet form or syrup with immediate reduction of cough reflex without affecting respiration. It is still available as medication in most European and Asian countries [38,39].

Anti-Tubulin Activity

Microtubules structures are involved in cell division; they are highly dynamic cytoskeletal fibers composed of tubulin subunits, i.e. α-tubulin and β-tubulin heterodimers arranged in the form of thin filamentous tubes. Noscapine shows its effect by slight suppression of both the growth and shortening of microtubules. To check whether Noscapine affects tubulin polymer ratio in cells, cell extracts containing cytoskeletal polymeric tubulin were incubated with different concentrations of Noscapine, i.e. 1, 10, 100 μM. The polymeric tubulin % in cells treated with Noscapine was determined using Western Blot method and was found to be 58, 59 and 59%, respectively [40].

Naik et al. indicated the binding site for Noscapine ligands using docking studies either close to or overlapping with the colchicines binding site [41]. Based on computational studies, Noscapine binding pocket of tubulin was found to be hydrophobic. The di-substituted brominated derivatives of noscapine, 9-Br-7-OH-Nos, 9-Br-7-OCONHEt-Nos, 9-Br-7-OCONHBn-Nos, and 9-Br-7-OAc-Nos were recently reported by Ram C. Mishra et al. [42], and their chemotherapeutic efficacy on PC-3 and MDA-MB-231 cells were investigated. It was found that these derivatives have higher tubulin binding activity than Noscapine and affect tubulin polymerization.

Anticancer Activity

Non-Small Cell Lung Cancer

Noscapine enhances the antitumor activity of gemcitabine in an addictive to synergistic manner against Non-small cell lung cancer (NSCLC) through apoptotic and antiangiogenic pathways [43]. The combination index value (<0.59) was indicative of synergistic behavior between noscapine and gemcitabine, thus suggesting the potential benefit for the use of combination treatment for treatment of NSCLC. The Noscapine and Gemcitabine combination treatment decreased cancer volume by maximum percentage as compared to single-agent treatment.

Similarly, the efficacy of Noscapine and Cisplatin combination was examined in vitro in H460 and A549 lung cancer cells and in vivo in murine xenograft lung cancer model [44]. The combination index value (<0.6) demonstrated the synergistic effects of noscapine and cisplatin, which resulted in tremendous increase in percentage of NSCLC cell death, increase expression of p21, p53, cleaved PARP, Bax, and decreased expression of Akt, cyclin D1, Bcl2, PARP. Such findings also suggested the potential benefit for the use of Noscapine and Cisplatin combination therapy for treatment of small lung cancer cells.

Triple-Negative Breast Cancer

Noscapine significantly increased the antitumor activity of Doxorubicin in an additive to synergistic manner against triple-negative breast cancer cells (TNBC) through inactivation of anti-angiogenic and NF-KB pathways [45]. The Noscapine and Doxorubicin combination treatment caused increase in the volume of apoptotic cells effectively. The Flow cytometry and cytotoxicity analysis of the Docetaxel in Noscapine pretreated MDA-MB-231 cells displayed 3.0-fold increase in cell death and about 30% increase in no of late apoptotic cells [46].

Noscapine when used in combination with docetaxel, activated p38 and JNK pathways. The noscapine exposure would significantly upregulate the p38 phosphorylation. Docetaxel showed

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down regulation in the expression of surviving, pAKT, and bcl-2 in noscapine pre-treated cells. The anti-migration effect of Docetaxel was significantly increased by noscapine pre-sensitization. The anti-fibrotic and chemo-sensitization effect of noscapine significantly enhanced anti-tumor effect of Docetaxel against TNBC. Moreover, Noscapine in combination with Docetaxel also has the potential to overcome multidrug resistance of TNBC even at low dose [47].

In-vitro and in-vivo results suggested that the Noscapine in combination with Docetaxel formulations inhibited the proliferation of both wild type and the drug-resistant TNBC cells. The potential of microtubule compounds to inhibit TNBC growth can be exploited to overcome drug resistance of TNBC cells. The killing of Docetaxel treated drug-resistant cells was more prominently observed in Noscapine pre-treated cells than without Noscapine pre- sensitization. Also, Br-TMB-Nos targeted tubulin via S-phase arrest instead of G2/M arrest [48]. Far-UV CD spectra suggested that the helical stability of tubulin was disrupted by the presence of Br-TMB-Nos.

The noscapinoid promoted the binding of colchicine to tubulin, altered the tubulin's surface configuration as well as slightly decrease polymer mass of microtubule. The Br-TMB-Nos was tested for three cell lines (HeLa, PANC-1, MDA-MB-231), out of which it suppressed clonogenicity of MDA-MB-231 cell line and, displayed most inhibition of this cell viability. The presence of this drug did not affect DNA and cellular microtubule.

Ovarian Cancer

There are two types of microtubule affecting agents, one those which bundle and polymerize microtubules and the other those which decrease the polymeric chain or depolymerize microtubules [49]. However, the major issues such as low aqueous solubility, toxicity, and drug resistance, severely hampered the clinical success of microtubule affecting agents [50]. Although the patients show good initial response to such agents but mostly patients relapse and did not respond to the same agents at the later stage. Simple and successful chemotherapy become complex and difficult due to multidrug resistance, which is most common problem in chemical biology research nowadays.

There are numerous factors that contribute to drug resistance such as upregulation of bcl-xL and bcl-2, overexpression of MDR1 and increased DNA repair [51]. Toxicity poses another major challenge to successful chemotherapy. This is because the antimicrotubule agents perform other functions such as axonal transport and cytoplasmic organization, in addition to their role in the chromosome's movement during mitosis. The agents, such as taxane and vinica alkaloids, are associated with several toxicities such as alopecia, peripheral neuropathy, and gastrointestinal toxicities.

Such aspect of toxicity is due to the lack of specificity for dividing cells. Considerable efforts have been made in last few decades to discover new and effective antimicrotubule agents having same mechanism of action to the preexisting drugs (such as paclitaxel, docetaxel, and vinica alkaloids) [52-54] but with better pharmaceutical features. Based on the systematic screening of structurally similar antimicrotubular agents, opium alkaloid noscapine was identified as the microtubule-targeting agent [55]. Noscapine effectively inhibited the proliferation and induced apoptosis in both paclitaxel-resistant and paclitaxel-sensitive human ovarian carcinoma cells (Figure 3).

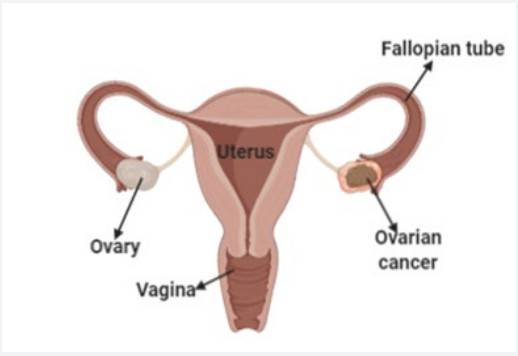

Figure 3: Ovarian Cancer.

This result is in good agreement with the assumption that noscapine binds to tubulin at the site different from the paclitaxel binding site. The noscapine exhibited non-inhibitory effect on the tubulin-binding by paclitaxel. Unlike other antimicrotubule agents, Noscapine does not inhibit or promote polymerization. In other words, even the high concentration of noscapine does not alter total polymer mass of the tubulin [56]. Noscapine arrest mitosis by causing changes to steady-state dynamics of microtubule assembly and this was done by increasing the period spend by microtubule in attenuated phase. This feature of noscapine ensures that noscapine would not affect other cellular events like axonal transport and cytoplasmic distribution.

Besides, the high dose of noscapine it did not affected the neurons, the post-mitotic cells. Noscapine causes little or no toxicity to small intestine, heart, bone marrow, kidney, spleen, and didn't inhibit oral immune response in mice [57]. The antimicrotubule agent causes apoptotic cell death as the result of alteration

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of normal physiological balance in microtubule dynamics. The noscapine causes JNK activation among all three human ovarian carcinoma cell lines, one-1A9 and other two tubulin mutant cell lines i.e., 1A9PTX22 and 1A9PTX10, while the paclitaxel induces JNK activation only in one parental ovarian cell line-1A9. These findings suggest that the mutations neither hinder the interaction of noscapine with tubulin nor the downstream effects that leads to apoptosis.

9-nitro-nos effectively inhibited cell proliferation of ovarian cancer cells especially the cell lines that showed multidrug resistance. 9-nitro-nos arrested progression of cell cycle at G2/M phase, followed by apoptosis. Nitro analog of Noscapine was found to be more effective against paclitaxel resistant variant 1A9/PTX22 than over parental ovarian cancer cell line-1A9 [49]. The IC50 value obtained for the drug-resistant variant was lower than that of parental ovarian cancer cells. 9-nitro-nos have binding pocket different from paclitaxel binding site. Hence, 9-nitro-nos displayed great sensitivity to drug-resistant cells.

The combination of chemotherapy and cytoreductive surgery has increased the survival time span of patients and decreased the mortality rate due to ovarian cancer. Some cases have become resistant to DDP-centered chemotherapy; majority of these cases account for gynecologic cancer deaths [58].

The survival rate of patients who are treated with DDP is seriously reduced due to cancer reoccurrence, development of drug resistance and toxic side effects of DDP therapy [59]. The drug resistance induced by DDP in ovarian cancer cell lines might be related to DAN repair dysfunction, abnormal cell cycle progression, drug metabolism disorder, and inhibition of apoptosis. DDP resistance could be stimulated in cancer cells by decreasing the p53 and Bax expression and enhancing expression of Bcl-2 and XIAP [60-61]. New combination regimens have become targets to overcome chemo resistance and to improve response rate of patients. Small molecule compounds such as noscapine and its nitro derivative, 9-nitro-nos effectively inhibited proliferation of paclitaxel resistant ovarian cancer cells [49,50].

This result proposes the effective use of noscapine to sensitize the chemo resistant ovarian cancer cell to DDP. Out of several factors that contribute to drug resistance, α subunit of HIF-1 has attracted great attention. Although the exact role of HIF-1 in cancer development is still controversial, but the various reports regarding its role suggested that HIF-1 allows the proliferation and survival of tumorous cells through its angiogenic properties and their transactivation during cancer progression. Several oncogenes, Hypoxia, and growth factors regulate HIF-1α and the inhibition of this protein complex by small molecule provides an effective therapeutic goal.

Various non-specific inhibitors of HIF-1α such as geldanamycin [62], 2ME2 [63], topotecan [64,65], 103D5R [66], rapamycin, bevacizumab [65] have recently shown effective anticancer activity. Under hypoxia-mimicking conditions, noscapine efficiently downregulated HIF-1α levels and significantly suppressed transcriptional activity of HIF-1. The downregulation of MDR1 and HIF-1α by noscapine was associated with DDP induced apoptosis [67]. Wenjing Su et al. reported that the noscapine decreases the transcriptional activity of HIF-1 and HIF-1α protein levels in C13K cells [67].

HIF-1α degradation was stimulated by noscapine through proteasome pathway and its degradation abolished MDR1 overexpression. Such effect forms the basis for chemosensitization by small-molecule compounds such as Noscapine. Under hypoxic conditions, noscapine inhibited the proliferation of C13K cells in concentration and time-dependent manner. The noscapine can reverse the chemo resistance of C13 K cells induced by hypoxia at very low concentration when given along with DDP. The antitussive agent Noscapine inhibited HIF-1 and HIF-1α regulated gene products and as a result, shows the potential to modulate the chemosensitivity of ovarian cancer cells to DDP.

Noscapine inhibited the proliferation of both DDP-sensitive SKOV3 and DDP-resistant ovarian cancer cell line SKVO3/DDP [68]. Low concentration of noscapine in combination with DDP effectively increased the toxicity of drug DDP to SKOV3/DDP cells line, enhanced cell apoptosis, and altered cell morphology. The anticancer activity of noscapine might be due to increased cytotoxicity caused by the coordinated effect of noscapine and DDP. The combined treatment with noscapine and DDP decreased the percentage of SKOV3/DDP cells in S phase and increased their percentage in G2/M phase. Both in-vivo and in-vitro experiments showed that noscapine enhanced DDP-mediated apoptosis, decreased the mRNA and protein level of XIAP, NF-jB, surviving and increased the mRNA expression of caspase-3. Hence the combination treatment of noscapine and DDP promoted apoptosis in DDP-resistant ovarian cancer cell SKVO3/DDP by controlling the expression of caspase-3, surviving, XIAP, and NF-jB.

Conclusion

Noscapine has poor absorption, limited water solubility, and short biological half-life; all such properties restrict its development as a prominent oral anticancer drug [69,70]. Novel water-soluble analogs of Noscapine such as 9-bromonoscapine and 9-aminonoscapine contained positively charged quaternary ammonium group and negatively charged sulfonate group. In addition to antitussive activity, Noscapine also has the great potential to treat wide range of cancers. Noscapine showed synergistic effect with another anti-tumor treatment. Although high dose of noscapine produces side effects such as abdominal discomfort and nausea, its usual dose does not produce any noticeable untoward effect [71].

The noscapine and its analog subtly modulate the microtubule dynamics rather than affecting monomer-polymer ratio. The potential ability of noscapine and its derivatives has been enhanced via nanoscale-based delivery system, such as noscapine loaded magnetic nanoparticle, Human serum albumin nanoparticle, and

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enveloped gelatin nanoparticle [72-75]. More research should be carried out on these compounds to explore new modifications increasing efficacy of drug delivery system and to identify more effective combination of noscapine or its analog with targeted agents to design clinical trials and preclinical studies.

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