Review Article

An overview on various types of anticancer drugs and their drug-drug interactions: Melphalan, 5-fluorouracil, and hydrazine

Syed Tazib Rahaman[1]*,Ruhita Pentakota[2], Praveen Vasireddy[3]

ABSTRACT

In this review article we primarily try to give more importance in knowing about various drug interactions with anti cancer drugs such as Melphalan, 5-Fluorouracil and Hydrazine which help in increasing their efficiency of action on tumor cells. As it is a review article we collaborated all the methodologies which were utilized drug combination studies which were used various research scholars. Results and discussion: This review is the therapeutic effects which are involved due to various drug combinations. Drug interactions occur in Pharmacokinetic and Pharmacodynamic levels. There are varied adverse effects which can be caused due to some of the Drug interactions Thus, systematic knowledge on Drug interactions particularly in every levels of absorption, elimination, transport and drug metabolism which may help in preventing these Adverse side effects. Combinations of dexamethasone with melphalan helped in treatment of POEMS syndrome. Melphalan also is helpful in Liposomal Drug delivery systems. One of the studies also proved the efficiency of Intraviteral and Sub-conjunctival injections in killing tumor cells. Cyclophoshamide pretreatment along with High dose of melphalan also helped in increase in efficiency of drug action on tumor cells. High dose of melphalan has also been proved to help in treatment of Neuroblastoma. We could also know the importance of carrier like PLGA by performing Biological evaluation of 5-Fluorouracil. Combination of Capaciatabine along with 5-FU helped in treatment of Oesophageal canecr. Studies on hydrazine proved to act as cancer causative agents. Oxaliplatin when given in combination with 5-FU helped in treatment of metastatic colorectal cancer. 5-FU loaded with microsponges helped in treatment of Colon cancer. Thus all these studies performed helped in providing efficient drug for treatment for various types of cancers.Thus there is an alarming need to perform studies on various relevant drug-drug interactions to treat a specific disease which would help in provision of treatment for any kind of disease which is affecting the patient.

KEY WORDS: 5-fluorouracil, Anticancer drugs, Drug-drug interactions, Hydrazine, Melphalan, Synergistic effect

INTRODUCTION

In this review article, we primarily try to give more importance in knowing various drug interactions with anticancer drugs such as melphalan, 5-fluorouracil (5-FU), and hydrazine which help in increasing their efficiency of action on tumor cells. In one of the recent studies, it was revealed that cells which are infected with microbes such as *Mycoplasma hyorhinis*[1] help in protecting tumor cells from action of anticancer drugs, and thus, it is necessary for us to create a very much effective drug to kill tumor cells by surpassing all the obstacles which come in between.

Anticancer drugs are those type of drugs which help in killing cancer cells or suppress the growth of cancer cells. There are primarily 2 stages after the treatment with anticancer drugs, they are induced prolong remission and palliation. Induced prolong remission leads to disappearance of macroscopic and microscopic features of cancer, but there would be persistence of the disease, whereas palliation leads to prolongation of life in several cases of patients suffering with breast cancer, ovarian cancer, and endometrial carcinoma. In accordance to their chemical structure, anticancer drugs are classified as alkylating agents, antimetabolites, antibiotics, plant extracts, and hormones. Alkylating agents consist of nitrogen mustard, ethylenimine, alkyl sulfonate, nitrosoureas, triazene, and methylhydrazine. Antimetabolites consist of folate antagonist, purine antagonist, and pyrimidine antagonist. Antitubulins, topoisomerase-1-inhibitor, topoisomerase-2-inhibitor, and antibiotics like bleomycin mitomycin are a part of cytotoxic drugs. Blocking of nucleic acid synthesis directly influences the structure and function of

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Department of Phrmacology, Gitam Institute of Pharmacy, Gitam University, Visakhapatnam, Andhra Pradesh, India

***Corresponding author:** Syed Tazib Rahaman, Gitam Institute of Pharmacy, Gitam University, Visakhapatnam, Andhra Pradesh, India. Phone: +91-7702149861. E-mail: tazib.research@gmail.com

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DNA, interference on protein synthesis, and influences hormone homeostasis on the basis of their biochemical action. According to phase specificity, anticancer drugs are classified as cell-cycle specific agents (CCSA) and cell-cycle non-specific agents (CCNSA). There are several targeted drugs such as tyrosine protein kinase inhibitor (imatinib and nilotinib), endothelial growth factor (EGF), receptor inhibitors (gefitinib, erlotinib, and cetuximab), angiogenesis inhibitors (bevacizumab and sunitinib), and progesterone inhibitors (bortezomib). Drugs such as glucocorticoid drug, estrogen receptors modulators, aromatase inhibitor, androgen antagonist, progesteron drug, and GnRH inhibitors are those which bind with hormone receptors to block the hormones which result in inhibition of tumor growth cells.

Alkylating agents contain highly reactive carbonium ion intermediate which transfer alkyl group to cellular macromolecules. Cisplatin, carboplatin, and oxaliplatin are anticancer drugs which help in the treatment of metastatic testicular and ovarian tumors along with lung, bladder, esophagus, hepatic, and gastric tumors. Antimetabolites are said to be S-phase specific drugs that are structural analogs of essential metabolites which interfere with DNA synthesis. Pyrimidine antagonist is said to have antineoplastic, antifungal, and anti-psoriatic properties. 5-FU is an analog of thymidine. 5-FU itself gets incorporated to RNA and thus interferes with RNA synthesis. Cisplatin and Oxaliplatin help in synergizing the 5-FU action. Malignant cells mostly spend a longer time in G1 phase of cell cycle. Most of the anticancer drugs affect the action on those drugs which are traversing the cell cycle (CCSA), whereas cell cycle non-specific agents sterilize tumor cells to know whether the cells are in a state of cycling or rest in G_0 Compartment.

Melphalan

Melphalan is considered to be a type of chemotherapy drug which is classified under the nitrogen mustard alkylating agents [Figure 1]. It is a phenylalanine derivative belonging to mechlorethamine. Being an alkylating agent, it causes linkages between DNA strands which leads to inhibition of DNA and RNA synthesis. Melphalan administration leads to many side effects such as nausea, oral ulceration, and bone marrow suppression and many other minor side effects such as rashes, hair loss, intestinal pneumonitis, itching, and irreversible bone marrow failure. These side effects causes decrease in WBC count and also leads to Anemia.

There is no standard treatment for POEMS syndrome as it leads to rare plasma cell disorder. This syndrome leads to high levels of increase in levels of serum vascular EGF (VEGF) which further caused extravascular volume overload, organomegaly, and hemangioma.

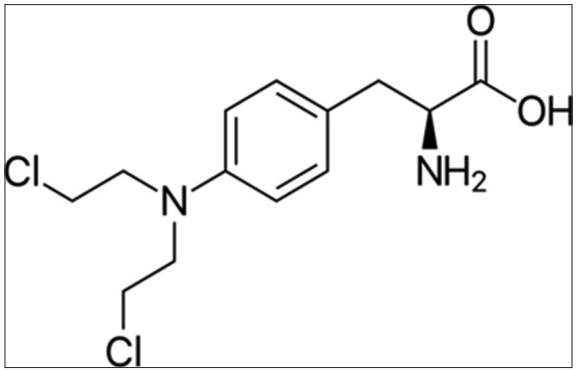

Figure 1: Melphalan

This syndrome finally leads to progressive peripheral neuropathy. Thus, to prevent the damage what this syndrome is causing a combination of melphalan along with dexamethasone (MDex) which showed low toxicity, a study done by Li *et al.*[2] was performed on 40 patients who are suffering with this syndrome. 9 of all the patients received high doses of melphalan by peripheral blood stem cell transplantation (SCT) method and remaining all the patients received low doses of melphalan. All the patients are made to receive 12 cycles of MDex treatment. Around 80% of the patients showed hematologic response, 38% showed complete remission, and 41% showed partial remission. Overall neuropathy limitation scale was used in this study to measure the outcome of the syndrome in patients. The presence of MDex also leads to increase in cytokine level which further causes a reversal of neuropathy. The results showed a dramatic decrease in median serum VEGF levels from 1047 pg/mL to 312 pg/ml. All patients are alive and free of neurological relapse after the median follow-up time of 21 months according to this study. This study proved that MDex in combination with melphalan provides effective treatment for newly diagnosed POEMS syndrome.

Melphalan which is a drug having poor stability and its ability to undergo rapid hydrolysis which makes the drug inactive was made to get encapsulated into liposomes which are made of egg phosphatidylcholine and cholesterol which had an average entrapment efficiency of melphalan of about 8%.

A study which was performed by Xie *et al.*[3] calculates the results by administering injections of melphalan and liposomal–melphalan on the left leg of rats. In the case of melphalan injection, there was no difference observed between ipsilateral and contralateral nodes, whereas in case of liposomal-melphalan injection, the liposome concentration in ipsilateral nodes was 200- and 100-fold higher than that in plasma and contralateral nodes, respectively.

Pretreatment of cyclophosphamide, cytosine arabinoside, and low-dose melphalan may prevent the

effect of high-dose melphalan (HDM) (Melph) on our body. When studies were done on mice, high dose of melphalan killed animals in various cases, but low-dose melphalan protected the intestinal epithelium in one of the rarest cases with the help of microcolony assay. Experiments when conducted in the case of tumor-bearing mice showed that pretreatment with cyclophosphamide did not lead to a reduction of toxicity of melphalan to the Lewis lung carcinoma. By the study performed by Millai *et al.*,[4] the effect of various pretreatments regarding the reduction of toxicity of large doses of Melph was reported. The reaction between clonogenic cells in marrow and intestinal epithelium was made to combine with cyclophosphamide (Cyclo) and Melph through which experiments were analyzed and investigated. The results showed that Melph killed 8/10 of animals on an average. High doses of Melph proved to be very much dangerous to animals which were tested. A dose of 50mg/kg of Cyclo helped in the survival of animals at least in some of the intervals at each dose level. The study relating to the effect of Melph pretreatment on intestinal epithelium proved that there is a correlation between crypt survival and animal survival. The study of survival of marrow stem cells after various doses of Melph also proved that there is no evidence that pretreatment with cyclo altered the sensitivity of stem cells with respect to Melph. There was recovery of bone marrow stem cells after 15mg/kg of Melph was added to all animals including those animals which had already undergone addition of 50mg/kg Cyclo 2 days before. Thus, the animals which were given pretreatment were completely back to normal, whereas the animals with no pretreatment were only 10% normal. The peripheral blood leukocyte count was initially very low in mice, and after addition of 50 mg/kg cyclo at the end of 6th day, there were 4 times the number of blood leukocytes found in mice which were used in the experiment. The Lewis lung tumor cells showed sensitivity to Melph. This study also proved that, due to addition 50 mg/kg of cyclo before Melph, there would be prevention of altering of the sensitivity of cholinergic tumor cells.

A study which was performed by Condomines *et al*.[5] tried to bring out a window after autologous SCT (ASCT) and HDM in the treatment of tumors by evaluating T-cell lymphopenia and measuring the immune cytokine concentrations such as IL-6, IL-7, and IL-15 plasma concentrations. The results showed a dramatic increase in IL-7 and IL-15 plasma levels which was inversely correlated to absolute lymphocyte count. The results also showed the activation of CD-3 cells which are present in ASC graft which was followed by death when cultured without cytokines. Thus, this proved that cytokines are very much essential in the growth of CD-3 cells which are very much essential in cancer cell death. Thus, along with ASCT and addition, HDM before cytokine concentration may act as a window in enhancing the survival rate of the patient and proliferation of polyclonal T cells. The study also proved that patients who received CD34+cell-selected grafts had significantly delayed CD4 and CD8 T cell recoveries by the day 100 than patients receiving unselected autografts.

In another study, a group of 12 children with advanced neuroblastoma were detected with their capability of producing an initial response to chemotherapy using cyclophosphamide/vincristine/adriamycin along with high dose of melphalan. This high dose of melphalan was combined with the process of autologous marrow grafting and given to the child. The results showed that procedures carried out without marrow grafting led to dangerous marrow and mucosal toxicity, but there were no treatment-related deaths caused during the study. 63.36% of children after experiment showed decrease in maximum diameter of primary tumor, 54.54% of children showed complete response, and survival rate of all autografted patients is more than 28 months. Thus, this study done by Pritchard *et al*.[6] proved that autologous marrow grafting helped in the treatment of chemotherapy.

Another study which was done by Shah *et al*.[7] tried to know the efficiency of intravitreal and subconjuctival administration of melphalan in the treatment of retinoblastoma. The results after 3 weeks of intravitreal injection showed a substantial decline of tumor size. Intratumoral hypoxia showed a significant decline in hypoxia after 1 week followed by intravitreal (IV) injection. Thus, this proved that IV and subconjunctival route of administration of melphalan lead to a dramatic decrease of tumor size than that of other routes of administration like intra-arterial route. This clearly signifies an important tool being uncovered which improves the efficiency of the effect of melphalan along with a reduction in time for reducing tumors, hypoxia, and vasculature with respect to the patient.

Immunoglobulin light chain amyloidosis has become one of the most threatening diseases which is spreading worldwide in a faster rate as monoclonal light chains get deposited in the organs which ultimately leads to death. The study performed by Cibeira *et al*.[8] explained the effectiveness of having hematological complete responsiveness (CR) in patients who are suffering with AL amyloidosis rather than much practiced SCT and a high dose of melphalan. This study also found out a very effective median event survival rate and overall survival (OS) rate of patients who all did not showed CR. Although there is a lot more research to be done, the potential of CR in treatment of AL amyloidosis has come to limelight

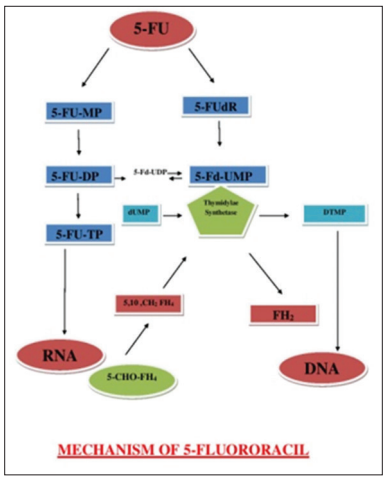

Figure 2: Mechanism of 5-fluorouracil

only because of this study carried out.

5-FU

According to the study which was conducted by Nair et al.[9],Nanoscale devices were mostly used for drug delivery systems which further helps in evaluation of antitumor efficacy of 5-FU which was entrapped by poly(D-L-Lactic-Co-glycolic acid) (PLGA). According to this study this mechanism was based on the combination of chemical components present in PLGA [Figure 2]. It is a combination of 50–50 and 90–90 monomers synthesized by double emulsion method and their evaluation done in glioma (U87MG) and breast adenocarcinoma (MCF7) cell lines. This study is done with an aim of developing a drug delivery system for evaluation of antitumor which produces a drug of small size with 5-FU which is binded with PLGA due to the presence of chemical components in it. PLGA contains two types of monomers, they are 50–50 monomers and 90–90 monomers produced by double emulsion method. The process involved in breaking of molecules that provides energy to the molecules were performed by using different diffraction techniques that were viewed through 5-FU.

A study was conducted by Veer *et al*.[10] which proved that a network meta-analysis (NMA) was helpful in evaluating the efficacy and safety of 5-FU and capecitabine. This mechanism was also helpful in S-1-based first-line treatment of advanced esophagogastric cancer in Asian and Western patients. Direct and indirect data for OS and progression-free-survival were combined on the hazard ratio (HR) scale using random effects NMA and calculated as combined HRs and 95% credible intervals (95%). Advanced esophagogastric carcinomais one of the major causes for the cancer deaths. Fluoropyrimidines are used for the initial treatment of esophageal gastric cancer. Along with fluoropyrimidines, 5-FU is also used for the initial treatment of advanced esophageal cancer. Capecitabine is mostly prescribed in the African countries. Fluoropyrimidines are combined with platinum-based antineoplastic drugs like taxane. When the comparison is done between the efficiency of capecitabine and s-1 based regimens, the most suitable drug which could be used to treat Asian patients was found to be s-1. When the fluorouracil was made to be compared with the efficiency of capecitabine, then capecitabine showed better drug action in both Asia and Western peoples because it combines with grade foot syndrome which is highly effective. Capecitabine is given by oral administration and s-1 is administered through intravenous administration for the patients who cannot administer drugs orally as they can be infused with fluorouracil. This study concludes that capecitabine was not suitable drug to be used for the treatment of Asian patients as it had a high amount of toxicity.

A study which was done by Davidov[11] reveals the prognosis in the patients suffering with metastatic colorectal cancer as the quality of life. It is a poor although palliative chemotherapy which is more effective than the best supportive care in improving survival and 5-FU is the most commonly used agent for treatment of metastatic CRC in the past 45 years. 5-FU is usually given in combination with leucovorin, a biomodulating agent that increases the binding of FU with to thymidylate synthetase, thereby increasing the inhibition of DNA synthesis and enhancing the antitumor effect of 5-FU. Colorectal cancer is also said to be a major cause for deaths of people in the African countries. The chemotherapy is the only technique that improves the quality of the life of people. Oxaliplatin is a platinum derivative. Oxaliplatin does not cause any problems in the kidney and blood like other platinum derivatives. The tumor in the patients was treated based on the blood samples weight and the patients response to the drugs and therapy. The tumour response is also divided based on their response. The classification is also derived from the guidelines of the WHO. This study helped found the evaluation methodology between drugs such as oxaliplatin and 5-FU or leucoverine.

A study which deals with pharmacokinetic, biodistribution, and therapeutic efficacy of 5-FU was done by Udofot *et al*.[12] 5-FU, an antimetabolite of the pyrimidine analog type, remains the gold standard for chemotherapy of CRC, despite its poor response rate of 20% when used as monotherapy or improved the response rate to merely 45% when used in combination with other antitumor drugs by encapsulating 5-FU in a nanocarrier, the dihydropyrimidine dehydrogenase attack on 5-FU could be reduced or avoided and efficacy of 5-FU could significantly be improved while its associated toxicity would be greatly reduced. 5-FU is an antimetabolite which exerts its effect by inhibiting thymidylate synthetase (TS) with the help

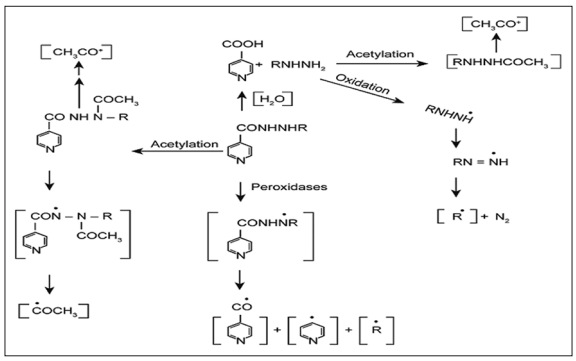

Figure 3: Metabolic activation of isoniazid[29]

of fluorodeoxyuridine monophosphate which results in thymidylate depletion and finally leads to apoptosis in cancer cells[13,14] though it still remains being plagued by efficacy and delivery issues such rapid systemic elimination, severe adverse effects, and lack of specificity. This study developed a 5-FU-loaded pH-sensitive PEGylated liposomal nanoparticle with surface modified with anti-EGFR (pHLNps-5-FU) so as to enhance 5-FU stability in systemic circulation by increasing its half-life and improve its therapeutic efficacy. 5-FU interacts with cells of nucleoside analogs that mimic the metabolite structure. 5-FU-treated animal is more efficient than free 5-FU which was found through *in vivo* and *in vitro* studies. Cytotoxicity inside the body of 5-FU was evaluated by trypan blue assay method. The drugs like fluorouracil are tested on the mice within the controlled environment by following the laboratory guidelines. The experiments which were conducted to find the difference between 5-FU and 5-FU PH PEgylated liposomal enzymes (PHLNP 5-FU) showed that 5-FU is more toxic than the PHLNP 5-FU. Cytotoxic effect of 5-FU which is exposed to HCT cells and blank liposyme was observed for about 24 hours and 48 hours, respectively. This study also proved that nanoparticle which can change their 5-FU PH LNP is more effective and shows less adverse effects than that of 5-FU.

Another study which was performed by Othman *et al.*[15] helped to develop Eudragit RS100-based 5-FU microsponges (MS) for treatment of colon cancer. HCT 116 and $CaCo_2$ cell lines were used for determination of cell viability by MTT assay. 5-FU with Eudragit RS100 was successfully formulated as sustained release manner and could be a substitution delivery method of 5-FU for oral anticancer treatment. 5-FU is a fluorinated pyrimidine antimetabolite converted within the cells into 5-fluorodeoxyuridine monophosphate which constrains the synthesis of DNA by inhibiting the cellular enzyme TS leading to blocking the conversion of deoxyuridine acid to thymidine.[16,17] Intravenous administration of 5-FU yields severe systemic toxic effects of gastrointestinal, blood complaints, and skin diseases, due to the 5-FU cytotoxicity on healthful human cells. MS are micro-sized particles with high porosity and unique ability for encapsulation of a wide multiplicity of pharmaceutical active ingredients. The purpose of the study was to prepare Eudragit RS 100-MS containing 5-FU using an emulsion solvent diffusion method for colon cancer treatment. The principles of MTT assay are based on the cleavage of the insoluble tetrazolium salt to a detectable colored formazan product by succinate-tetrazolium reductase enzyme that exists in the mitochondria and it is only active in the viable cells. When the drug-to-polymer ratio was increased, the entrapment efficiency was increased due to decrease the total drug lost at the steps of the fabrication process. Magnesium stearate was used as stabilizer to overcome the problem of coalescence flocculation of particles during solvent diffusion by the reduction of the phase tension between the formed MS and liquid paraffin. The results showed that the increase in polymer concentration resulted in increasing the particle size of MS. The release of 5-FU from MS was characterized by an immediate burst release followed by a slow release that oil in oil solvent diffusion represented a successful method of encapsulation of 5-FU with relatively high encapsulation efficiencies.

A study which was performed by Blandford *et al.*[18] proved that filtering surgery in glaucoma patients created an alternative aqueous pathway from the anterior chamber to the subconjunctival space. Failure usually is due to the proliferation of fibroblasts, which leads to scarring and subsequent blockage of the filter. Successful filtration in these patients primarily depends on a suppression of fibroblast, proliferation of 5-FU, NaH_2PO_4, and also on polyvinyl alcohol (98% hydrolyzed, 76,000–78,000 molecular weight). The concentration of 5-FU then was determined by HPLC analysis. A sustained release form of 5-FU can be expected to prevent the peak tissue levels obtained with SC injections. In this animal model, filters uniformly fail. Maintenance of a functioning filter in the present study suggests that this drug delivery system may be useful in high-risk patients. In humans, the lower intrinsic fibroblastic proliferation and the concurrent use of steroids could be expected to further improve outcome. A phase one clinical trial is underway.

Hydrazine

Acyl hydrazone derivatives based on naproxen and ibuprofen were synthesized throguh a three-step method in good yields in one of the studies done by Nakka *et al.*[19] All of the compounds synthesized were found to exist as a mixture of two rotameric forms in solution, for example, antiperiplanar (ap) and synperiplanar (sp) as indicated by their 1 h nuclear magnetic resonance (NMR) spectra. Hydrazones have attracted considerable attention in medicinal

chemistry due to their distinctive structural features and a wide range of pharmacological activities. This is exemplified by the synthesis and pharmacological evaluation of a large number of hydrazine derivatives against various pharmacological targets. This study tried to describe the synthesis, structure analysis, and *in vitro* pharmacological properties of a number of acyl hydrazone derivatives based on naproxen and ibuprofen. The compounds were found to exist as a mixture of two rotameric forms in solution. This study also established an E-configuration of the C=N bond unambiguously. The ibuprofen-based hydrazones showed superior cytotoxicity than that of naproxen. Finally, this study proved that this class of hydrazine derivatives presented an interesting profile for further experimental investigations, especially in the area of anticancer research.

In one of the studies done by AITamimi *et al.*,[20] the polymers were synthesized from polymerization of methyl acrylate, and then it was reacted with hydrazine hydrate in the presence of ethanol to prepare polymer. In this study, the new polymers were synthesized from polymerization of methyl acrylate and then reacted with hydrazine hydrate in the presence of ethanol to prepared polymer (b). This polymer was reacted with KOH, carbon disulfide (CS2), 10% hydrochloric acid, and ethanol as solvent to product polymer (c) and then reacted with hydrazine hydrate to prepared polymer (d) which form diazonium salt by reacted with NaNO2 and concentrated HCl at 0C0 to form polymer (e). Acetylacetone was added to the polymer (e) in basic media to form a product of azo heteropolymer, then reacted with hydrazine and their derivatives to form new heteroring on azo heteropolymer.All prepared polymers were identified by physical properties, fourier transform infrared, and some of them 1 h NMR.

From the past few decades, the field of chemical carcinogenesis has been focusing on the possible roles of synthetic chemicals in causing cancer to man. The aim of one of the studies done by Toth *et al.*[21] was to draw attention to both the synthetic and naturally occurring derivatives of hydrazine. The synthetic hydrazines in recent years were shown to produce tumors in animals, and therefore, they may play a role in the etiology of human cancer. A study done by Levenberg *et al*.[22,23] reported that the isolation of agaritine from A. bisporus was the most commonly eaten commercial mushroom in the United States. Preliminary toxicity studies with agaritine were performed in mice and published recently.[24,25] Gigliotti and Levenberg[26,27] also found an enzyme in the mushroom, gamma-glutamyltransferase, that catalyzes the breakdown of agaritine to L-glutamate and 4-hydroxy methyl phenylhydrazine. However, some of these chemicals such as hydrazine have undesirable effects, which lead to toxicity and convert into metabolic transformation [Figure 3], resulting in severe organ toxicity, tumor formation, and some cases death of the person. Hydrazine found in tobacco and edible mushroom. Hydrazine had derivatives such as isoniazid and iproniazid. Hydrazine is toxic and induces DNA damage.

Hydralazine

Hydralazine, which is a vasodilator, is one of the most intresting hydrazines in current use in medicine. It is one of the most important drugs for the management of high blood pressure and recently has garnered a significant amount of interest for the treatment of cancers. Hydralazine has also been found to inhibit iron containing prolyl hydroxylase enzymes, which are important for the induction of hypoxia-induced factor (HIF alpha) and VEGF.[28] HIF alpha is a critical target in cancer chemotherapy, and it is involved in tumor progression.[28]

Structure of hydralazine and formation of various reactive metabolites catalyzed either by metal ions or enzymes. Isoniazid is acetylated *in vivo* to acetyl isoniazid, which is rapidly hydrolyzed to acetyl hydrazine. Further metabolism of acetyl hydrazine by cytochrome P450 isozyme leads to the formation of reactive acetyl carbocation (CH3CO+), which binds to macromolecules.[30,31] It has been shown that the severity of hepatotoxicity parallels the covalent binding. Iproniazid is readily hydrolyzed *in vivo* to isopropyl hydrazine, and it has been reported that isopropyl hydrazine is rapidly metabolized by cytochrome P450 with the formation of reactive intermediates that covalently bind to proteins.[30,31] Isopropyl radical has been identified as the reactive species that covalently bind to cellular protein.[30-32] Isopropyl hydrazine has also been found to undergo acetylation, resulting in alkylation of proteins. Procarbazine is another anticancer drug which was used for the treatment of Hodgkins lymphoma, malignant melanoma, and brain tumors in children.[33,34] Procarbazine has been shown to be mutagenic in both bacterial and mammalian systems and has been reported to be carcinogenic in mice, rats, and monkey.[35,36] Procarbazine is a prodrug, and therefore, requires extensive metabolism for its activity. The metabolism of procarbazine is complex; it is been essential for its antitumor, mutagenic, and carcinogenic activities.

CONCLUSION

The various kind of combinations of interactions of other drugs with anticancer drugs such as melphalan and 5-FU has proved that there is definitely an increase in efficiency of drug action in killing tumor cells. Combination dexamethasone with melphalan helped in treatment of POEMS syndrome. Melphalan also is

helpful in liposomal drug delivery systems. One of the studies also proved the efficiency of intravitreal and subconjunctival injections in killing tumor cells. Cyclophosphamide pretreatment along with a high dose of melphalan also helped in an increase in efficiency of drug action on tumor cells. High dose of melphalan has also been proved to help in the treatment of neuroblastoma. We could also know the importance of carrier like PLGA by performing Biological evaluation of 5-FU. Combination of capecitabine along with 5-FU helped in the treatment of esophageal canecr. Studies on hydrazine proved to act as cancer causative agents. Oxaliplatin when given in combination with 5-FU helped in the treatment of metastatic colorectal cancer. 5-FU loaded with MS helped in the treatment of colon cancer. Thus, all these studies performed helped in providing the efficient drug for treatment for various types of cancers. These studies also helped us to know the importance of gaining knowledge about drug-drug interactions which would be very much useful for creating an effective combination of active drug for curing any type of threatening disease. Thus, there is an alarming need to perform studies on various relevant drug-drug interactions to treat a specific disease which would help in provision of treatment for any kind of disease which is affecting the patient.

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