Alkylation agents as chemotherapeutic agents

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Chemotherapy simply means the use of chemicals to treat disease by destroying microorganism or cancerous or tumor cells. Generally, chemotherapy acts by destroying rapidly dividing cells although the mechanism that leads to this differs. Several divisions of chemotherapy agents exist such as the anti-metabolites, plant alkaloids the topoisomerase inhibitors, anthracyclines and alkylation agents which are discussed in this paper. Generally, alkylation agents work by addition of alkyl groups to the guanine of DNA molecule at number 7 atom of imidazole group (Siddik, 2002).

Alkylation agent’s significance The name originates from their ability to alkylate several nuclophilic functional categories in certain cellular conditions. Examples of alkylation agents are carboplatin, oxaliplatin and cisplatin that work by covalent bond formation with specific carboxyl, sulphurhydril and phosphate groups in molecules of biological importance (Siddik, 2002). These are regarded as platinum-based alkylation agents. These platinum based alkylation agent are divided into first, second and third generations made up of cisplatin, caboplatin and oxaliplatin respectively.

They found important use in treatment of mesothelioma . They work at all stage of cell cycle and impair cellular DNA synthesis as well as transcption (Siddik, 2002). Cisplatin is used to treat lung and testicular cancers. Other alkylation agents include chlorambucil, mechlorethamine, ifosfamide and cyclophosphamide as well as procarbazine and bulsulphan. Alkylation agents are effective at all stage of cell cycle making them useful in treating wide

range of cancer especially the slow growing ones like solid tumor and leukemia.

All share biochemical mechanism although they may differ in their clinical effects. The significance of alkylation agents is not only seen in treatment of leukemia, lymphomas and solid tumors. They are also found significant in the treatment of non neoplastic conditions such as cyclophosphamide use in treatment of autoimmune disease . Pulse dose cyclophosphamide is used in lupus nephritis and other conditions like Wegener’s granulomatosis, multiple sclerosis and rheumatoid arthritis (Siddik, 2002).

Biakylating and Monoakylating agents: The biakylating agents are capable of reacting with two 7-N guanine residues. When these residues are in different DNA strands, there is resulting crosslinkage of DNA strands and this makes DNA double helix to fail to uncoil (Siddik, 2002). However, when the two guanine moieties are in same base strands, what occurs is known as limpet association of DNA to the drug molecule. Example of biakylating agent is Bulsuphan . On the contrary, monoakylating agents are only capable of reacting with one 7-N of guanine molecule.

Classical alkylation agents: These are termed alkyl groups and they include three subgroups which are: (a) the nitrogen mustards which include mephalan, ifosfamide, uramustine, chlorambucil, mechlorethamine and cyclophosphamide b) The nitrosoureas which are carmustine, streptozocin and lomustine c) the alkyl sulphonates such as bulsuphan. ? Alkylation-like agents: They lack alkyl group but destroy DNA. They are regarded as alkylation-like as they coordinate to DNA so as to interrupt DNA repair permanently.

They are the platinum based drugs such as cisplatin, oxaliplatin and carboplatin. They also bind at N7 position of guanine (Siddik, 2002) ? The Non-classical: Certain categories are termed non-classical such as altremine and procarbazine. Furthermore, sometimes the platinum based drugs are also regarded as non-classical. Nitrogen Mustards The nitrogen mustards are a group of DNA alkylation agents which are not specific . They are cytotoxic and have similar qualities to mustard gas, hence utilized as medicinal and chemical warfare agents.

Nitrogen mustards stockpiled by many countries in WW II serve as potent and useful blister agents. Nitrogen mustards suppress bone marrow production of red blood cells. The first nitrogen mustard developed was mustine with anti-neoplastic chemotherapeutic value. Other examples of alkylation agents in nitrogen mustardfamilyare mephalan, cholambucil, cyclophosphamide, uramustine and ifosfomide (Siddik, 2002). The likes of Bis (2-chloroethyl) ethylamine and Tris (2-choloroethlamine) are few nitrogen mustards used in chemical warfare.

Nitrogen mustard’s mode of action involves formation of aziridinium or cyclic aminium ion when the amine nitrogen displaces chloride at intermolecular level. This is then followed by alkylation of DNA centers by the azidirium group (Siddik, 2002). Malfunctioning of alkylation DNA is usual during replication (Pizzo & Poplack, 2006). They prevent cell division and by so doing cause abnormal base pairing. Also it is possible that more than a single alkylation groups may exist in each molecule .

In order words, these therapeutically useful alkylation agents are either bialkylating or polyalkylating agents. The damaging effect is comparable to

that which is seen with exposure of genetic material to radiation making it radiometric. Earlier, nitrogen mustards have been shown to form interstrand crosslinks (ICLs) and this formation takes place between N-7 of guanine residue in a 5'-d (GC) sequence, although it was later discovered that nitrogen mustards form a 1, 3 Interstrand crosslinks in the 5'-d (GNC) sequence.

For instance, cyclophosphamide (cytophosphane), a nitrogen mustard arise from oxazophorine group and exhibits their chemotherapeutic effects by its nitrogen mustard metabolite, phosphoramide which form both interstrand and intrastrand crosslinkages at N-7 position of guanine molecule causing cell death. Cyclophosphamide metabolite is usually produced in cell with low amount of ALDH.