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Review Article

Chemotherapy in Head and Neck Malignancy

Rumela Ghosh[1]*, Renita Lorina Castelino[2], Kumuda Rao[2], Baishwanar Banerjee[3] and Anasua Debnath[4]

[1]Private Practitioner, Department of Oral Medicine and Radiology, A B Shetty Memorial Institute of Dental Sciences, Nitte University, Mangalore, Karnataka, India

[2]Lecturer, Department of Oral Medicine and Radiology, A B Shetty Memorial Institute of Dental Sciences, Nitte University, Mangalore, Karnataka, India

[3]Post Graduate Student, Department of Forensic Medicine and Toxicology, Kasturba Medical College, Manipal University, Manipal, India

[4]Post Graduate Trainee, Department of Prosthodontics and Crown and Bridge, Manipal College of Dental Sciences, Manipal, India

***Corresponding Author**: Rumela Ghosh, Private Practitioner, Department of Oral Medicine and Radiology, A B Shetty Memorial Institute of Dental Sciences, Nitte University, Mangalore, Karnataka, India.

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Abstract

In the present scenario, despite rapid development in the medicinal research field, cancer is emerging as a challenge for society. Various treatment modalities are devised for the treatment of head and neck cancer, chemotherapy being one of them. Chemotherapy drugs exert their effects by interfering with the processes involved in cell division. In the present article we discussed about the various chemotherapeutic drugs, their mechanism of actions and side effects.

Keywords: *Chemotherapy; Alkylating Agents; Antimetabolites; Myelosuppression*

Introduction

Head and neck malignancy [HNC] mostly comprises of epithelial cancers of the upper respiratory and the digestive tract (URDT), including the, oral cavity, paranasal sinuses, pharynx, nasal cavity and larynx [1]. Most of head and neck malignancy i.e. around 90% are squamous cell carcinomas [2]. Around 44,660 people in the United States, and 76,000 in Europe are diagnosed with head and neck malignancy per year [3,4]. The overall incidence and prevalence of oral cancer is rising despite various advances in diagnosis. In the present scenario percentages of mortality and morbidity is 6.6 per 100,000 and 3.1 per 100,000 in men and 2.9 per 100,000 and 1.4 per 100,000 in women [5]. However during the last 20 years, treatments modalities for head and neck carcinoma have changed dramatically mostly due to the advances of novel approaches such as combined modality therapy as well as improvements in surgical and chemotherapeutic agents. Chemotherapy is a systemic treatment unlike radiotherapy or surgery and can be administered as a primary treatment or as a multidisciplinary approach.

In this article we will mostly focus on using chemotherapeutic agents in the management of HNC. The treatment of head and neck malignancy by chemotherapy has a relatively recent history. The response to methotrexate (MTX) was reported long back in the early 20th century which subsequently encouraged researchers to carry out the studies further [6]. It was the most extensively used cytotoxic drug for head and neck malignancy cancer before 1978 [7].

Chemotherapeutic drugs are classified according to their source or their action on the tumor cells and include alkylating agents, antimetabolites, antibiotics, alkaloids, hormonal agents, nitrosoureas, targeted cancer drugs and miscellaneous agents [8]. It can be used in 4 different ways:

1. Neoadjuvant (Induction) chemotherapy
2. Concurrent (Concomitant) chemotherapy
3. Adjuvant (Post-op) chemotherapy
4. Palliative chemotherapy

Chemotherapy agents are highly toxic, henceforth utmost precautions are needed during preparation and administration of the drugs.

Alkylating agents

They basically act by interacting with the DNA causing cross-linking reactions or strand breaks and substitution reactions.

Cisplatin i.e. Cis diamminedichloroplatinum (CDDP) has been strongly used in the treatment of malignancy since 2.5 decades, but still the biochemical mechanism of action is not clearly understood. According to the recent accepted paradigm about cisplatin, the mechanism of action is that the drug induces its cytotoxic properties through binding to nuclear DNA and subsequently interferes with the DNA replication mechanisms and/or normal transcription [9].

In recent times it is noted that Cisplatin as a single agent is not above or superior to Methotrexate in terms of survival or response [7]. Most importantly the multi-agent chemotherapy in general is associated with improved response rates than single agent alone and Platinum containing combination regimens have been proven with the highest response rates.

Alkylating Agents	Side Effects
Cisplatin	Myelosuppression, neurotoxicity, nephrotoxicity, nausea and vomiting, hypokalemia and hypomagnesemia
Carboplatin	Nausea and vomiting, ototoxicity, neurotoxicity, bone marrow suppression, hyperuricemia
Chlorambucil	Myelosuppression and interstitial pneumonia
Cyclophosphamide	Myelosuppression, anorexia, alopecia, stomatitis, gonadal suppression, nail hyperpigmentation, nausea and vomiting

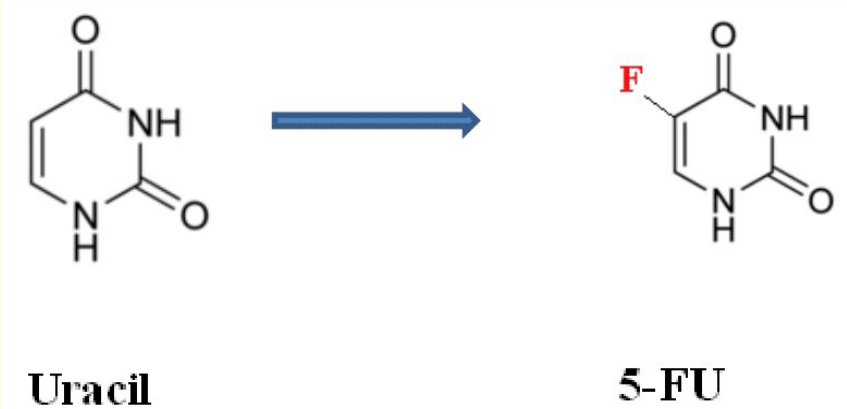
Table 1: *Table showing various alkylating agents and their possible side effects [10].*

Antimetabolites

They act by interfering with the synthesis of new nucleic acid. They are cell cycle specific and highly toxic to the proliferating cells.

Methotrexate is one of the most widely used drug of this group for chemotherapy. It is a structural analog of folic acid which binds to and inhibits dihydrofolate reductase and decreases the intracellular folate co-enzymes, which in turn decreases the production of thymidylic acid and eventually depressed the DNA/RNA synthesis and finally causes cell death [11].

5 – Fluorouracil (5-FU) is a pyrimidine analog which has a stable fluorine atom in place of hydrogen at the position 5 of the uracil ring.



Like Methotrexate it mostly deprives the cells of essential precursors of DNA synthesis. The primary mode of action of this drug is mediated via inhibition of thymidylate synthetase. 5-FU is initially converted to fluoride-deoxyuridine monophosphate (FdUMP) which competes with deoxyuridine monophosphate (dUMP) for thymidylate synthase, leading to a lack of thymidine which results in imbalanced cell growth and cell death [12].

Antimetabolites	Side Effects
Methotrexate	Mucositis, vomiting, nausea, alopecia, diarrhea and myelosuppression is the most common and renal toxicity in higher doses.
5-Fluorouracil	Mucositis, bone marrow suppression, nausea and vomiting, alopecia and anorexia
6- Mercaptopurine	Nausea and vomiting, myelosuppression, anorexia, hepatotoxicity, hyperpigmentation.
6-Thioguanine	Anorexia, stomatitis, vein irritation, nausea and vomiting, hepatotoxicity, myelosuppression

Table 2: *Table shows various antimetabolites and their side effects [13].*

Antitumor Antibiotics

They act on the DNA to disrupt transcription of DNA and RNA. They are not cell cycle specific but the effects of this drugs are more pronounced in the S or G2 phase.

Bleomycin are glycopeptide antibiotics isolated from *Streptomyces verticillus*. Bleomycin has been found to inhibit the DNA synthesis while RNA and protein synthesis are comparatively less affected. In the cell cycle, Bleomycin usually produces a blockage in the early G2 phase. It cause fragmentation of the DNA that results in their cytotoxic activity. Bleomycin has two major domains in its structure. One portion interacts with the DNA and the other binds with iron. Both iron and oxygen are required for the degradation of DNA by the drug. It binds Fe^{2+} and DNA by intercalation between GT or GC base, and acts as a ferrous oxidase (Fe^{2+} Fe^{3+}) resulting in production of oxygen free radicals that cleave the DNA [14].

Dactinomycin i.e. Actinomycin D are orange to red antibiotic metabolites of various species of *Streptomyces*. It inhibits DNA directed RNA synthesis in low concentrations and at higher concentrations DNA synthesis is also prevented. Although all types of RNA are affected, but the ribosomal RNA is more sensitive. After binding to the double stranded DNA, it permits RNA chain initiation but blocks the chain elongation. Binding to the DNA takes place in the presence of guanine. It appears that phenoxazone chromophore region of the drug inter-

calates between bases in the DNA and that the 2-amino group of the guanine is important in the formation of a stable drug -DNA complex. This blockade is responsible for the cytotoxic effect [15,16].

Antitumor Antibiotics	Side Effects
Bleomycin	Pulmonary fibrosis, anaphylaxis, pneumonitis, alopecia, stomatitis fever, chills, nausea and vomiting.
Dactinomycin	Renal, hepatic abnormalities, GI ulcerations, proctitis, anemia, blood dyscrasias and esophagitis, nausea and vomiting, stomatitis.
Mitomycin	Serious cumulative bone marrow suppression, thrombocytopenia and leukopenia that can contribute to the development of overwhelming infectious disease. Irreversible renal failure as a consequence of hemolytic uremic syndrome. Occasionally adult respiratory distress syndrome has also been seen.
Doxorubicin	Myelosuppression, vesciation, cardiotoxicity, stomatitis alopecia, nausea and vomiting, hepatic damage.

Table 3: *Table shows various antitumor antibiotics and their side effects [17-19].*

Squamous Cell Cancers	
Primary Systemic Therapy and Concurrent Radiotherapy (combined)	
REGIMEN Cisplatin (preferred) [22,23]	Dosing Days 1, 22 and 43: Cisplatin 100 mg/m^2 IV + concurrent radiotherapy 2Gy/day to a total of 70Gy.
Cetuximab(Category 1) [24]	Day 1: Cetuximab 400mg/m^2 loading dose over 2 hours, 1 week before radiotherapy, plus Day 7: Begin radiotherapy with 7 weekly infusions of cetuximab 250mg/m^2.
Carboplatin + infusional 5-FU (Category 1) [25,26]	Days 1-4: 5-FU 600mg/m^2/day as continuous IV infusion + carboplatin 70mg/m^2/day IV bolus. Repeat every 3 weeks for 3 cycles (given concurrently with radiotherapy).
5-FU + hydroxyurea [27]	Day 1: Hydroxyurea 1,000mg PO every 12 hours (11 doses/cycle) and 5-FU 40 0mg/m^2/day continuous IV infusion, plus radiotherapy: 70Gy, delivered in 35 fractions; 1 fraction delivered daily Monday - Friday. Concurrent radiotherapy and chemotherapy every other week for total treatment duration of 13 weeks.
Cisplatin + paclitaxel [27]	Day 1: Paclitaxel 30mg/m^2 IV, plus Day 2: Cisplatin 20mg/m^2 IV. Repeat cycle every week for 7 cycles, plus radiotherapy: 70Gy, delivered in 35 fractions; 1 fraction delivered daily Monday - Friday.
Cisplatin + infusional 5-FU [28]	Day 1: Cisplatin 60mg/m^2 over 15 minutes; plus Days 1-5: 5-FU 800mg/m^2 by continuous infusion; plus Days 1-5: Radiotherapy: 2Gy repeated every other week for 7 cycles.
Carboplatin/paclitaxel (Category 2B) [29]	Day 1: Paclitaxel 40 - 45 mg/m^2/week and carboplatin 100 mg/m^2/week; prior to radiotherapy: 70.2Gy at 1.8 Gy/fraction/day for 5 days/week.
Weekly cisplatin (Category 2B) [13,30]	Day 1 - 28: Cisplatin 40 mg/mg^2 IV over 30 minutes weekly; plus Days 1 - 38: Radiotherapy (5 fractions/week): 1.8Gy single dose (up to total dose of 50.4Gy); plus Days 22 - 38: Boost radiotherapy: 1.5Gy/day (up to 19.5Gy) in addition to regular dose. Booster doses to be given at least 6-hours after regular dose (total tumor dose of 69.9Gy.) OR Day 1 - 28: Cisplatin 40mg/mg^2 IV weekly; plus Days 1 - 40: Radiotherapy: five fractions of 1.8 Gy/week (up to total dose of 54Gy); plus Days 25 - 40: Boost radiotherapy: 1.5 Gy/day (up to 19.5Gy) in addition to regular dose. Booster doses to be given at least 6-hours after regular dose.
Primary Chemotherapy With Postoperative Chemoradiation	
Cisplatin (Category 1 for high-risk) [31-34]	Days 1, 22 and 43: Cisplatin 100mg/m^2 IV + radiotherapy.
Induction Chemotherapy/Sequential chemotherapy [21]	
Docetaxel + cisplatin + 5-FU (Category 1 if induction is chosen) [16-18]	Day 1: Docetaxel 75 mg/m^2 IV + cisplatin 75 mg/m^2 IV, plus Days 1 - 5: 5-FU 750 mg/m^2 continuous IV infusion. Repeat every 3 weeks for 4 cycles.
Paclitaxel + cisplatin+ infusional 5-FU [35]	Day 1: Paclitaxel 175 mg/m^2 over 3 hours Day 2: Cisplatin 100 mg/m^2; plus Day 2 - 6: 5-FU 500 mg/m^2 continuous infusion Repeat every 3 weeks for 3 cycles.
Paclitaxel + cisplatin+ infusional 5-FU [35]	Day 1: Paclitaxel 175 mg/m^2 over 3 hours Day 2: Cisplatin 100 mg/m^2; plus Day 2 - 6: 5-FU 500 mg/m^2 continuous infusion Repeat every 3 weeks for 3 cycles.

Table 4: *Table shows the cancer treatment regimens below that include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.*

Conclusion

The recent advances in molecular biology, including the human genome project has expanded our knowledge and has allowed for the introduction of targeted therapies for malignancy. The future aspect of treatment of head and neck malignancy lies in the hand of gene therapy and immunotherapy [20,21].

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