REVIEW

Molecular Pathogenesis of Oral Cancer – An Overview

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Abstract

Introduction: The oral cavity is the primary site of origin for oral cancer, a subtype of head and neck cancers. Surgery is still the most common form of treatment for oral cancer, but it is linked with severe deformity, the inability to perform daily mouth tasks, psychosocial stress, and extensive recovery. The use of immunological therapies, which are still experimental and immature, to improve the body's capacity to identify cancerous tissue as a foreign substance is also prevalent. Although there has been significant progress in the treatment of oral cancer, more research is still needed to understand the complex heterogeneous nature of the disease and to identify the molecular mechanisms that underlie the emergence of resistance to therapeutic agents and how to combat it in order to increase patient survival and quality of life.

Materials and Methodology: Scientific databases were searched for the literature and relevant articles were selected or the review.

Conclusion: This review provides an overview of oral cancer, risk factors, symptoms, molecular biology of the cell cycle, oncogenesis and tumour suppressor genes, biology of invasion and metastasis, emergence of metastasis, and reasons why chemotherapy and radiotherapy fail. It also discusses the biology of invasion and metastasis.

Key words: Oral Cancer, Molecular Biology, Oncogenes, Mutations

Introduction

In India, oral cancer (OC) is the most prevalent malignancy, accounting for 50–70% of all cancer-related deaths and having the highest prevalence in Asian nations. Despite the fact that many individuals are unaware of it, oral cancer ranks as the sixth most frequently fatal malignancy globally. The oral cavity and, specifically, the oral mucosa, are affected by malignant neoplasms in this text[1]. Studies of "head and neck cancer" are commonly cited when talking about concerns related to oral cancer because this illness has many similarities to squamous cell carcinomas that develop elsewhere in the upper aero-digestive tract and have similar risk factors. As a matter of fact, more than 95% of all oropharyngeal malignancies reported to the SEER (Surveillance, Epidemiology and End Results) programme of the National Cancer Institute of the United States Public Health Service registries in the USA between 1973 and 1987 were squamous cell carcinomas, with the exception of lesions of the salivary glands, gingivae, nasopharynx, nasal cavity and sinuses[2].

Around 300,000 persons are newly diagnosed with oral cancer each year worldwide, and two-thirds of these are from developing nations, according to epidemiological studies from different nations. Global fluctuation in the exposure to the use of risk factors like alcohol and cigarettes is the cause of the annual incidence rate of mouth cancer. Additionally, the USA reports about 8000 fatalities from mouth cancer each year[3].

Pharyngeal and oral cancers both ranked seventh in occurrence in the European Union, where 70,000 new cases are recorded annually. According to estimates, mouth cancer will develop in 1.17% of Europeans over their lifetimes.

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France, Hungary, Slovakia, Slovenia, Brazil, and Southeast Asia are reported to have higher oral cancer incidence rates. Oral carcinoma accounts for about 40–50% of all malignancies in India, Bangladesh, Sri Lanka, and Pakistan, which are considered high-risk nations[4].

The World Health Organization identified India as the oral cancer epicentre of the world and said that mouth cancer is a significant health issue and burden in this nation. Around 70,000 new cases and 48,000 reported fatalities from oral cancer occur each year. Furthermore, 40% of all cancer-related deaths in India are caused by oral carcinoma[5].

Between the ages of 40 and 70, mouth cancer has been found to affect men more frequently than women globally. It is projected that the number of cancer cases in India will rise from 1.46 million in 2022 to 1.57 million in 2025. The crude rate of incidence per 100,000 people in the country for the year 2022 is 100.4; for males, it is 95.6, and for females, it is 105.4. Male and female lung and breast malignancies, respectively, continue to be the most common cancer locations.

According to estimates, there would be 1,03,371 occurrences of lung cancer in 2022, ranking in the top five primary causes for both men and women. In 2020, the current predictions for cancer in India grew by 5%. In developing countries such as India, the ratio of male to female is closer to 1:1. The predicted total number of cancer cases and crude incidence rate in India for 2022 was 14,61,427 (100.4 per 100,000). More cases were expected to occur in women (7,49,251 (105.4 per 100,000) than in men (7,12,176 (95.6 per 100,000). The top five locations with the highest incidence of cancer in both genders were the digestive system (2,88,054), respiratory system (1,43,062), genital system (2,18,319), breast (2,21,757), oral cavity and pharynx (1,98,438), and genital system (2,18,319). According to estimates, the top five cancerous locations in men were the mouth (8.4%), tongue (5.9%), prostate (6.1%), lung (10.6%), and stomach (4.8%).

In females, the predicted top five sites of cancer incidence were the ovary (6.2%), breast (28.8%), cervix (10.6%), corpus uteri (3.7%), and lung (3.7%). While thyroid (3.6%) and gallbladder (2.7%) cancers were in the top ten among females but not among males, liver cancer (3.9%) was one of the top ten malignancies in men but not in women. Estimated percentages of the top five cancer-causing sites in India by age group (0–14, 15–39, 40–64, and 65+) for the year 2022. For both boys (29.3%) and girls (24.3%) in the children (0–14) year age group, lymphoid leukaemia is the most common site, followed by the brain nervous system (NS) (12.4% for boys and 14.3% for girls). Male mouth (12.0%), tongue (8.8%), brain NS (7.0%), myeloid leukaemia (6.5%), and non-Hodgkin lymphoma (NHL) (5.9%) are the most common sites in the adolescent and young adult (15–39 years old) age group; female leading sites are breast (27.3%), thyroid (12.2%), ovary (7.3%), cervix (7.1%), and myeloid leukaemia (3.7%).

For men in the 40–64 age range, the mouth (10.9%), tongue (7.3%), and lung (11.0%) were the most common sites. In females, the most common sites were the breast (33.0%), cervix (12.3%), and ovary (6.5%); cases in this age range were highly prevalent in both genders (3,41,230) and in females (4,25,918). Prostate (12.3%) was the second most common site in males over 65, after lung (13.1%). Lung cancer ranked highest among males over 40 years of age, while breast cancer topped the list for females.

GLOBOCAN has calculated the cancer incidence in India for 2020 by utilising cancer incidence in five continents and ASIR from 27 PBCRs of data from 2012 to 2014. The cervix, ovary, and corpus uteri are the three female genital organs that rank second and third among the top five cancers in females, respectively. Males were confined to three locations for tobacco-related cancers: the tongue, mouth, and lungs[6,7,19].

RISK FACTORS OF ORAL CANCER

Risk factors are the substance(s) or agents that increase the likelihood of contracting a specific disease. Tobacco use, alcohol use, cardiovascular and respiratory conditions, poor diets and nutrition, non-communicable diseases, obesity and being overweight. Viruses can alter cells and cause them to become malignant, some infections are more likely to result in cancer. This includes infections with the human papilloma virus (HPV), which are responsible for about 70% of cases of cervical cancer. Hepatitis B (HBV) and hepatitis C (HBC) viruses can also cause non-Hodgkin lymphoma and liver cancer. Age and genetics are other factors that affect the risk of cancer in addition to these controllable risks. This is due to the fact that the longer a person lives, the greater the likelihood that they have been exposed to cancer-causing substances and the longer the window of opportunity for genetic alterations in their cells.

Periodontal Disease; A Risk Factor for Oral Cancer

Worldwide, cancers of the head and neck area (HNC) cause over 650,000 cases and 330,000 deaths per year. Squamous cell carcinoma is the most prevalent histology of OC, one subtype of HNC that affects the lips and oral cavity (SCC).

With about 354,000 new cases annually worldwide, cancer of the lip and oral cavity ranks as the 16th most prevalent form in the Globocan 2018 database. The literature's findings unequivocally demonstrate that males are more likely than females to have OC. According to recent studies, periodontitis linked to poor OH may contribute to the development of OC. Ageing is a common risk factor for periodontal disease, and there is a correlation between the frequency of oral SCC and ageing.

Periodontal disease were found to have a higher chance of acquiring OC in several large prospective trials. Existing research in the literature provides compelling evidence that periodontal disease may operate as a stand-alone risk factor for OC. Patients with clinical attachment loss larger than 1.5 mm had a higher incidence of oral tumours, according to a cohort research by Tezal et al. According to Al-Hebshi et al.'s observations, oral neoplasms frequently exhibit the isolation of periodontal pathogens such Porphyromonas gingivalis and Fusobacterium nucleatum. Porphyromonas gingivalis, one of the Gramnegative anaerobs that belong to the red complex consortium, was suggested to have a significant involvement in the development of OC based on a comprehensive bibliographic review that included studies published up till 2020.

The research that is now available also suggests that significant inflammatory mediators that may be connected to

carcinogenesis are present in periodontal disease. A persistent systemic inflammation is maintained in periodontal disease, raising levels of pro-inflammatory cytokines and acute phase proteins in plasma. Strangely enough, inflammation itself can lead to oxidative damage to the DNA of the cell, which is linked to the formation of a malignant lesion. Several research examined the relationship between periodontal disease, or OC, and tooth loss. Even after the criteria were changed to account for alcohol and tobacco use, the majority of them still discovered a significantly elevated risk of OC linked to higher tooth loss or other periodontitis-related factors.

Additionally, recent research indicates that changes in the oral microbiota associated with periodontal disorders may foster the growth of oral SCC. Regular dental appointments and upkeep of the OH can help avoid periodontal disease, a persistent inflammatory illness. A chronic inflammatory process is brought on by poor dental hygiene and the plaque accumulation that follows, which fosters the development of OC. When periodontitis reaches more advanced stages, the risk of OSCC rises.

The risk of OC may be reduced by maintaining periodontal health and keeping an eye on people whose lifestyle choices put their teeth at danger. Periodontal disease has been linked to an increased risk of oral cancer, dry snuff use, exposure to ultraviolet (UV) radiation from sunlight while working outside, and lip cancer, which is the most common type of cancer among outdoor workers. Mouthwash use and discomfort from improperly fitted dentures are two untested or debatable risk factors for oral cancer. Oral cancer has been linked to immunosuppressed people, and people with enzyme deficiencies in the xenobiotic metabolising pathway may be at increased risk of developing the disease[7,20].

Signs And Symptoms Or Clinical Features Of Oral Cancer

- A lip or mouth sore that doesn't heal within two weeks
- A white or reddish patch on the inside of your mouth
- Loose teeth
- A growth or lump inside your mouth
- Mouth pain
- Ear pain
- Difficult or painful swallowing, speaking or moving your jaw or tongue.
- Patches inside mouth that you can't scrape away. These patches may be pre-cancerous conditions.
- The following conditions all appear as patches in your mouth and throat, but they're different colors:
  - Leukoplakia: These are flat white or gray patches in your mouth or throat.
  - Erythroplakia: These are slightly raised or flat red patches. These patches might bleed when scraped.
  - Erythroleukoplakia: These patches are red and white
- Rough spots or crusty areas on your lips, gums or in the mouth.
- Areas in mouth that bleed for no obvious reason.
- Numbness
- Tenderness on your face and neck or in your mouth that occur without apparent cause
- Unintentional Weight loss
- Chronic bad breath
- Bleeding
- Mobility of teeth
- Problems in breathing
- Difficulty in speech
- Dysphagia
- Problems using from prosthesis, trismus, and paraesthesia.
- Occasionally patients may present with cervical lymphadenopathy without any other symptoms.
- In terminal stages, patients may develop skin fistulas, bleeding, severe anaemia and cachexia.
- Decreased mobility of the tongue
- Voice changes
- Cervical tumours were more common in tumours at the tongue base[21].

Molecular Biology of The Cell Cycle

Proto-oncogenes and tumour suppressor genes are important genes in head and neck malignancies (TSGs). The process of cell division can be seen as a series of checkpoints or transitions where certain requirements must be satisfied in order for the cell to move on to the following stage.

These checkpoints can be more easily understood if they are seen as the results of signaling pathways that started when cells recognized DNA damage. A checkpoint is activated to stop the cell cycle from continuing when DNA is damaged.

This apparently stops either incorrect chromosomal segregation during mitosis or the cell from reproducing the damaged DNA templates in S phase (GI checkpoint) (G2 checkpoint). Higher eukaryotes' cells can only divide when they are exposed to the required extracellular stimuli, such as cytokines or hormones that circulate in the blood, or when they come into contact with other nearby cells or a substrate. Otherwise, the cells stay in G0 and are in a quiescent condition.

Cyclin-dependent kinases are the chemicals that direct cells through the various cell cycle phases[8]. Cyclin-dependent kinases (Cdks) and the cyclins that regulate them are important regulators of cell proliferation because they catalyse the transition into S phase and into mitosis. As the cycling cells move through the G1 phase, a number of cyclin/Cdk complexes amass. The tumour suppressor protein pRb is hyperphosphorylated when cyclin D/Cdk4 is active in the middle to late stages of the G1 phase. Cyclin A and cyclin B build up in cells during the S and G2 stages. Entry into mitosis is triggered by the activation of these enzyme complexes. cyclins and their related cyclin-dependent kinases (Cdks). (Adapted from Zelenka1 and Gao1*).

CARCINOGENS

Anything that has the capacity to cause cancer is considered a carcinogen. Certain carcinogens, including sunlight's UV radiation, are found in nature. Others come from man-made sources, including smoke from cigarettes. The majority of carcinogens work by causing DNA mutations in cells. Certain types of cancer can be caused by different carcinogens. On the other hand, exposure to carcinogens can increase a person's

risk of getting some types of cancer.

Chemical Carcinogens: These are carcinogens that humans emit into the atmosphere when they pollute, such as when they smoke cigarettes, produce industrial byproducts, or drive.

Physical Or Environmental Carcinogens: The environment contains these carcinogens. Physical carcinogens include radiation from X-rays and other radioactive materials, as well as UV rays from sunlight.

Viruses That Can Cause Cancer: These viruses fall within this category. Hepatitis B, Epstein-Barr, and the human papilloma virus (HPV) are a few examples.

Alcohol, Asbestos, Engine exhaust, Formaldehyde, Processed Meat, Radon, Tobacco, UV rays, Arsenic, Chloroform, Coal dust and Emissions, Cobalt, Epstein-Barr virus, Estrogen-Progestogen combined oral contraceptives, Estrogen therapy for menopause, Hepatitis B, Hepatitis C, HPV, HIV type 1, Mineral oils, Nickel, Outdoor air pollution, X-rays and gamma rays. However, examples of carcinogenic chemicals are also found among agricultural chemicals (e.g., pesticides, herbicides, and fungicides), industrial chemicals (e.g., aromatic amines, vinyl chloride, benzene, and chromium compounds), atmospheric pollutants (e.g., polycyclic aromatic hydrocarbons resulting from incomplete combustion of fossil fuels), contaminants in drinking water (halogenated organic compounds produced during water chlorination), some medications (including some anticancer drugs, estrogens, and analgesics), plants such as cured tobacco, cooked meats (which produce polycyclic aromatic hydrocarbons and heterocyclic aromatic amines), and mycotoxin-contaminated foods (e.g., aflatoxins)[5].

Oncogenes and Tumor Suppressor Genes: Proto-oncogenes are genes whose overexpression or mutation causes uncontrolled cell growth and cancer. These genes' protein products have been identified to be crucial for normal cell growth signaling. Oncogenes are gain-of-function mutations that can modify the cellular structure by altering just one of each gene's two copies[9].

Activation of Oncogenes

p53GENE: The most significant TSG, dubbed the "Guardian of the Genome," is the p53 gene. plays a crucial role in the course of the cell cycle, cellular differentiation, DNA repair, and apoptosis. It is known that over 70% of oral cancers have mutations in this gene. In 20% of cases of oral cancer and 22% of premalignant oral leukoplakia lesions, the heterozygosity of the p53 allele has been observed to have been lost. Point mutations, deletions, and interaction with viral and cellular proteins are some of the methods that might inactivate a gene.

A protein's structural integrity is changed by point mutations. Reduced p53 expression and loss of protein function are caused by deletions[9].

According to immuno-histochemical investigations, over-expression can occasionally happen even when the cancer itself is p53 negative in the mucosa that surrounds a carcinoma that appears to be normal. For instance, smoking has been demonstrated to increase p53 in mucosa that is otherwise normal. The p53 gene is gradually altered during the course of tumour growth, and at least four separate molecular processes may be involved. p53 mutations, deletion of the wild-type allele, increase in the number of aneuploid chromosome copies, which increases the dosage of the mutant gene and amplified p53 gene.

mdr-1GENE: The over expression of the mdr-1 gene, which produces the P-glycoprotein transmembrane protein with a molecular weight of 170 kDa, is frequently linked to multidrug resistance (MDR) in human cancer (P- gy). Jain and associates evaluated P-gy expression in various stages of oral cancer progression using immunohistochemistry and flow cytometry. When compared to normal oral mucosa, oral dysplasia showed a significantly higher level of P-gy expression, suggesting that changes to the protein may be one of the crucial early steps in oral carcinogenesis. When compared to oral mucosa from cancer-free patients, cancer patients' tumor-adjacent oral mucosa displayed a high expression of P-gy, which may be a sign of field cancerization[9].

CD44GENE: The CD 44 gene has attracted early attention due to its potential for early cancer detection and for the investigation of genetic abnormalities related to neoplasia. According to reports, a variety of growing epithelial malignancies have altered expression of CD 44's conventional and mutant forms (e.g. gastrointestinal, renal, pulmonary). The majority of the examined malignancies (notable exceptions include head and neck squamous cell carcinomas and neuroblastomas) have higher levels of the CD 44 protein isoforms in tumour tissue than in non-cancerous control tissue. The tumor's diverse expression is only found in tumour cells.

Furthermore, oral squamous cell cancer and severe dysplasia both exhibit a down-regulation of the CD 44 variation. When compared to other cancer cells, which almost universally exhibit an elevated expression of CD 44 molecules, including variations this low expression in oral malignancies may signal a high spreading potential[10].

Chromosomal Imbalances: Oral squamous cell carcinoma's onset and progression have been linked to genomic anomalies on chromosomes 3 and 17. Additionally, there are hints that a 3p deletion and violent biological behaviour are related. According to Tsuji et al., oral squamous cell carcinomas had considerably higher rates of polysomy 3 and 17 when compared to controls. The degree of polysomies did not, however, appear to be correlated with clinicopathologic variables including tumour differentiation, illness stage, DNA ploidy, or clinical prognosis. Patients with advanced head and neck cancers have a significant rate of loss of heterozygosity (LOH) for tumour suppressor genes[11].

Bcl-2GENE: Bcl-2, which stands for B-cell lymphoma/leukemia-2 gene and is the main regulator of apoptosis, is frequently found to have abnormalities in its structure or expression in numerous human neoplasms. The gene is necessary to prevent normal cells from dying off (apoptosis). Nuclear envelop, mitochondrial membrane, endoplasmic reticulum, and a number of normal tissues all contain Bcl-2 oncoproteins. Bcl-2 proteins are often restricted to basal or proliferative cells. Follicular B-cell lymphoma is the only tumour in which the Bcl-2 gene has a structural defect (translocation

t); the deregulation mechanism in other neoplasms is mainly unclear[12].

DNA Content: The influence of DNA patterns in neoplastic cells on prognosis has been the subject of various research. Static as well as flow cytometry has been used for the measurement of the DNA patterns. Static cytometry is more effective at identifying morphologically irrelevant cells. The S phase can also be evaluated more effectively with flow cytometry.

The frequency of DNA non-diploid tumours among head and neck carcinomas has ranged in the literature from 41% to 86% depending on measuring methods or the type of DNA classification. Non-diploid tumours typically exhibit less differentiation than DNA diploid tumours[13].

Epiderma Lgrowth Factor Receptor: The numerous soluble polypeptide growth factors influence nearly all cell types' development and differentiation, and by binding to particular cell-surface receptors, they mediate a variety of biological consequences. When receptors are activated, a series of messenger proteins form an intracellular signalling pathway. A malignant behaviour is thought to be best predicted by growth factors, their receptors, or aspects of their intracellular signalling system. In its physiological function, the epidermal growth factor receptor (EGFR) regulates a variety of non-mitogenic activities, such as changes in cellular metabolism, biosynthesis, differentiation, and angiogenesis[14].

Proteinases: It is still highly hypothetical what precise roles matrix metalloproteinases and proteinase inhibitors play in neoplastic invasion and metastasis. Although it has often been noted that these proteins are elevated in a variety of neoplasms, it is unknown which, if any, of these proteins are essential for invasion and metastasis to occur. The examination of nuclear matrix proteins in squamous cell carcinoma of the head and neck is motivated by the knowledge that nuclear matrix undergoes distinctive changes during cell differentiation and that the transition from normal to malignant tissue is associated with specific nuclear matrix alterations. Nuclear matrix proteins that are absent from normal mucosa and are only found in squamous cell carcinomas have been reported to be connected with malignant transformation from normal oro-pharyngeal mucosa[15].

Cell surface carbohydrates: Numerous tumour cell lines have shown a clear relationship between sialylation and the ability to metastasize, and some glycosylation abnormalities are known to reduce the ability to metastasize. Given that carbohydrates play a role in metastasis, tumour cells with variable metastatic potentials are likely to have glycosylation patterns that differ in either quality or quantity. Studies on oral cancer indicate that the density of sugar residues in the cell membrane, in particular, may have a role in predicting the tumour's capacity for metastasis[13].

Role of Hpv in Oral Cancer: Human papillomavirus is linked to head-and-neck squamous cell carcinoma, Epstein-Barr virus is linked to nasopharyngeal carcinoma, and Kaposi's sarcoma-related herpesvirus is linked to oral Kaposi's sarcoma. These are the viral agents connected with oral cancers. Numerous human cancers, including those of the cervical, vulvar, vaginal, penile, anal, and head and neck regions, have been linked to HPV. It is a double-stranded DNA virus that is not enclosed. Eight genes, categorised as early (E) and late (L) genes, are encoded by its DNA genome. While the late genes, L1 and L2, encode the major capsid and minor capsid proteins, respectively, the early genes, E1, E2, E4, E5, E6, and E7, are crucial for the replication of the viral genome. The HPV life cycle begins when the virus infects undifferentiated basal squamous epithelial cells in the oral cavity as a result of damage or erosion. This allows the virus to transfer its DNA into the nucleus of the host cell. Important to the viral life cycle, the HPV E2 protein performs well-understood roles in transcriptional control, DNA replication initiation, and viral genome maintenance.

Major viral oncogenes, the E6/E7 of high-risk HPV, are involved in the conversion of growth-arrested differentiated epithelial cells into actively proliferating cells. High-risk HPV E6/E7 interact with a number of tumour suppressors and cyclin-dependent kinase inhibitors to cause abnormal cell cycles and proliferation. The tumour suppressor protein p53 is bound by E6 and a cellular ubiquitin ligase called E6-AP, which subsequently targets the protein for proteosomal breakdown and ubiquitination. Decreased transcription of p21, a cyclin-dependent kinase inhibitor (CDKI), which causes the differentiated epithelial cells to enter the S phase of the cell cycle, deregulation of DNA damage repair and cellular senescence, and inhibition of the pro-apoptotic functions of p53 are among the mediated effects of p53 destabilisation.

By attaching to the hypo-phosphorylated version of pRb preferentially, HPV E7 impedes the tumour suppressor protein pRb's ability to function. While the carcinogenic qualities of high-risk HPV E6 and E7 are strong, they are typically limited when the E2 protein is present. Deregulated production of E6 and E7 is linked to head-and-neck cancer and cervical cancer due to the integration of the HPV genome and deletion or disruption of the E2 gene. Furthermore, by transcription of persistent chimeric virus-cell mRNA in cervical and head-and-neck malignancies, integration can also result in significant expression of E6/E7 proteins. The integration of high-risk HPV into the host genome is thus a critical stage in the development of cancer[22].

A Genetic Progression Model for Head and Neck Squamous cell carcinoma:

It has been successful to compile a wealth of molecular, genetic, and biological data in order to create a model that closely resembles the colorectal model for the onset and course of head and neck squamous cell carcinoma. The progression of squamous cell carcinomas is believed to involve several clinical and histopathologic stages, each of which is accompanied by a succession of accumulating genetic changes. Fragile sites are extremely susceptible to breaking brought on by carcinogens including viruses, cigarettes, and alcohol. About 85% of head and neck squamous cell carcinomas have lost or disrupted their most prevalent fragile site in humans, FRA3B, which is at 3p[16].

Biology of Invasion and Metastasis: Brodland compared the three-stage carcinogenesis process (initiation-promotion-progression), which entails the conception, gestation, and birth of a malignant tumour, to childbirth.

Initiation: Caused by a number of different carcinogenic agents, such as pesticides or oncoviruses, and results in genetic changes. As mutational events are expected to happen often during the day for the skin and oral mucosa, initiation is extremely common. The altered cell's descendants could inherit the mutation if it survives and spreads. On the other hand, the majority of started cells never go past the initial mutation. For malignancy to progress, a second genetic mutation is required. Histologically speaking, the started cell and its companion cells can be indistinguishable[17].

Promotion: This mechanism is receptor-mediated and reversible. Initiated cells require interaction with a promoter to continue their clonal proliferation. By raising the number of started cells and, thus, the likelihood of a second genetic mutation, promotion raises the risk of progression. Regarding beginning, promotion does not always result in a malignant lesion and is occasionally avoided[17].

Progression: The histopathologic changes are easily visible by light-optic inspection in this step. An irreversible genetic mutation that results in progression is one that gradually develops a more malignant genotype and phenotype. The increase of genetic instability causes cells to grow faster, become more invasive, and adapt to foreign influences[17].

Advent of Metastasis

Detachment: By performing this move, the cell is able to function without the requirement for cell-to-cell communication and is set up for the various cellular adjustments that will occur during the metastatic phase.

Invasion And Intravasation: Cell attachment to the vascular basement membrane, enzymatic breakdown of surrounding tissue, and cell migration into the appropriately prepared tissue appear to be the three phases of invasion. The receptors that are particular for vascular basement membranes or interstitial cells, such as fibronectin receptors, are abundantly present on tumour cells as they adapt to invasion. The term "intravasation" describes the passage of a tumour cell past the vessel walls and into the bloodstream[18].

Circulation: Since most tumour cells die before entering stasis, this may be the step of the metastatic process that is most frequently rate-limiting. Physical (turbulence, shearing forces, collisions) and immunologic factors can cause cell death in the circulation.

Stasis: The majority of metastatic lesions are created through passive stasis and capillary bed lodging. However, the fact that both site-specific and non-specific patterns of metastasis seem to be independent of either passive mechanical implantation or site-specific receptors highlights the high adaptability of circulating tumor cells.

Invasion And Extravasation: A feasible metastasis does not always result from tumour stasis. After stasis, there must be invasion of the recipient tissues and extravasation via the endothelium walls.

Proliferation: Proliferation of a neoplasm in a foreign environment may not be conceivable, which is frequently a rate-limiting phase. Effective proliferation requires the tumour to produce angiogenic factors, autocrine growth factors, to be responsive to local growth hormones, and to be insensitive to local growth inhibitors[18].

Relationship Between DNA Pattern in Neoplastic Cells and its Prognosis: The DNA molecule is constantly being attacked by a range of endogenous and external genotoxic insults. When intracellular free radical oxygen species (ROS) arise as byproducts of mitochondrial respiration, endogenous damage can be caused by DNA base lesions such as hydrolysis (deamination, depurination, and depyrimidination), alkylation (6-O-Methylguanine), or oxidation (8-oxoG).

Normal cellular metabolism can also result in mutations, such as when deoxyribonucleotides (dNTPs) are mistakenly incorporated during replication. Physical sources of environmental damage include UV light, ionising radiation (IRs), and thermal disruption. Chemical sources include chemotherapeutic drugs, industrial chemicals, and cigarette smoke. The effects of these sources range from the creation of pyrimidine 6-4 pyrimidone photoproducts (6-4PPs) and cyclobutane pyrimidine dimers (CPDs) after UV exposure to the introduction of single and double DNA strand breaks upon IR treatment to the creation of inter- and intrastrand DNA crosslinks as a result of different chemotherapeutic drugs.

DNA lesions can change the double helix's basic structure, which can have an impact on transcription and replication. Incorrect lesion healing can result in genetic changes that are passed down to daughter cells and have a negative impact on an individual's health. The prevalence of numerous severe human disorders brought on by mutations in DDR genes serves as a reminder of the significance of DNA repair systems. It is true that changes in chromosomal aberrations and mutations can affect how a gene functions.

When tumour suppressor genes are inactivated or oncogenes are activated, unchecked tumorous cell proliferation results. When inherited flaws in DNA repair mechanisms result in heightened susceptibility to cancer, the fundamental function of DNA damage in the formation of cancer has come to light. It has long been known that DNA damage is a contributing component to the development of cancer. Erroneous repair of DNA can result in chromosomal aberrations or mutations that impact tumour suppressor and oncogene genes, causing cells to change malignantly and grow cancerous.

Mutations in different DNA repair mechanisms increase the risk of developing different types of cancer. But DNA damage is not only a major contributing factor to the development of cancer, it also remains a vital target for chemotherapy and radiation treatment. Gene-damaging drugs that cause DNA damage checkpoints have been used from the inception of cancer therapy to stop the growth and cause cancer cells to undergo programmed cell death. Significant advancements in cancer treatment will result from a deeper comprehension of the functions and interactions of the incredibly intricate DNA repair machinery. Different DNA repair processes identify and eliminate the damages. DNA damage checkpoints can cause cellular senescence, apoptosis, or stop the cell cycle if the damage is not repaired[23].

CAUSES OF CHEMOTHERAPY AND RADIOTHERAPY FAILURE

- It is important to note that the majority of these tissue markers may have prognostic significance in patients undergoing androgen deprivation and treatment, as they are not exclusive to RT and CT failure.
- One typical route used by PCa cells to pass through the prostate capsule and reach the extra-prostatic tissue is peri-neural invasion.
- Anatomic Factors Involved in Radio and Chemotherapy Failure: PCa cells placed at the limit of and outside the radiation leads to failure.
- The existence of undetected lymph node metastases was an independent predictor of recurrence and death in a multivariable analysis.
- Lymphatic invasion is the initial stage of lymphatic dissemination and lymph node metastasis.
- In solid tumours, tumour cell proliferation, resistance to apoptotic cell death, abnormal growth factor receptor expression, and hypoxia are considered reasons why therapies fail.
- Upregulation of AR expression in PCa cells that sustains AR signalling through the hypersensitive pathway under regular ADT.
- Increased intratumoral de novo production of testosterone and dihydrotestosterone (DHT) leads to enhanced ligand-dependent activation of the AR.
- Nonhormonal growth factor receptor-mediated activation of the AR (erb1/EGFR, erb2/HER2, etc.; outlaw route) without the need for a latch.
- Extension of the ligand specificity of AR mutants binding non-androgen steroids (progestins, oestrogens, etc.; promiscuous route).
- AR-independent processes (neuroendocrine (NE) differentiation, bcl-2, etc.) that avoid the AR (bypass pathway) to maintain growth and survival.
- Stem cell pathway-mediated prostatic cancer renewal provides a steady supply of tumour cell populations during ADT.
- Abnormal p53 accumulation in PCa tissue has been linked to poor outcomes and the progression of PCa. It is also mutated and upregulated in high-grade and metastatic disease.

SOME CHEMOTHERAPY FAILURE CAUSES

- Absorption, Permeability glycoprotein (P-gp), Food, Distribution, Evolutionary resistance, MRPs and MXR.

ALTERATION OF DRUG TARGET

- Methotrexate and 5-fluorouracil

MICROENVIRONMENTAL RESISTANCE

- pH, Oxygen, Glucose[24].

Passive Mechanisms: Liposomes can employ both passive and active targeting techniques to specifically target cancerous areas. Certain mutations can result in the body's cells proliferating uncontrollably, which can lead to cancer. The primary cause of liposomes' passive targeting of tumour tissues is the tumour microvasculature's endothelial cells' differing pore diameters from those of normal capillaries, which are "tighter." Consequently, an optimal targeting goal would be accomplished if liposomes were prepared with a size that permits extravasation in tumour tissues while preventing the carriers from leaving the capillaries in normal tissues. At tumour sites, enhanced permeability and retention effect (EPR) is an phenomena that occurs in addition to increased permeability. Increased blood capillary permeability in the impacted tissues and a significantly reduced fluid return to the lymphatic circulation are the characteristics of this condition.

Active Mechanisms: DNA repair procedures, removing unwanted drugs (cell membrane-bound pumps), drug detoxification inside cells (e.g. the glutathione system), Increased output, genetic up-regulation, and repair of a particular molecular injury, Quiescent clone proliferation to counteract the harm and eradication of other cells, improvement of cell survival through apoptosis control, selection and emergence of cell clones with resistance. (such as paradoxical drug resistance) by the production of topoisomerase in surviving cells.

A drug carrier can actively target a particular place on the body in a number of ways. A range of ligands are used to take advantage of any particular antigens expressed by cancer cells in order to accomplish the active targeting of cancer locations. As conjugating RNA A10 onto PLA-block-PEG co-polymers, the prostate-specific membrane antigen has been successfully targeted. This has resulted in enhanced medication delivery to prostate tumour tissue as compared to non-targeting nanoparticles. Binding to target cells and uptake by the RES are two kinetically competing processes in the case of immunoliposomes' active targeting. PEG chains have effectively prevented liposomes from being absorbed by RES, which has increased blood concentration and improved immunoliposome target binding[4,25].

Research For Selective Cancer Treatment Can Be Divided Into

Hypoxia-Selective Cyto-Toxins: Low oxygen levels in tumours are advantageous when therapeutic cytotoxicity and/or anticancer drug potentiation are targeted on hypoxic cells in solid tumours. Compared to oxygenating the cells or chemically sensitizing them to chemotherapy or radiotherapy, the death of hypoxic cells offers a better potential for therapeutic benefit. The ability of hypoxia-selective cytotoxins to increase the killing by common anticancer medications is a significant advantage.

Liposomes: The enhanced permeability and leakiness of tumour arteries have made it possible to target anticancer medications particularly to tumours using liposomes that have undergone specific modifications. The fact that the distribution of the liposomes is quite diverse and concentrated in the perivascular interstitium negates the appeal of permitting large tumour concentrations via liposomes[18].

Anti-Angiogenesis: Because it concentrates on a process that is largely unique to tumours, there is little systemic damage.

There is a closer proximity to tumour cells when an endothelial cell target is used. Drug resistance should not emerge because endothelial cells are genetically stable.

Gene Therapy: With the aim of selectively destroying cancer cells while protecting healthy cells, genetic material is introduced into cells via a number of approaches in this innovative anticancer therapy approach. Currently, either vector delivery and activity control or transgenic expression are used to achieve this selective death. The targeting of constructs to the tumour, as is the case with most types of gene therapy, is still a considerable challenge[19].

Conclusion

Oral cancer is a diverse, aggressive, and complicated disease. The most common forms of treatment include surgery, chemotherapy, radiotherapy, and immunotherapy either alone or in combination. Every form of treatment has its own setbacks. Surgery results in a considerable loss of oral capabilities, which is followed by numerous remedial procedures that result in significant deformity and a protracted road to recovery. This always causes loved ones to endure significant pain and suffering in addition to losing their sense of self-worth. In terms of cytotoxicity, tolerance, non-specificity, resistance, and loco-regional relapse, other therapies like chemotherapy, radiation, immunotherapy, etc. have limits. Resistance can be reduced and treatment can be better adapted to the patient in this way. We have covered the main oral cancer pathogenesis-related factors in this review. Novel genetic abnormalities need to be explored further so that more potent personalised targeted medicines can be developed and made available to patients.

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