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ASSOCIATION OF BACTERIAL INFECTION, RESISTANCE OF ANTIBIOTIC AND CANCER CHEMOTHERAPY: AN ESCALATING THREAT IN CANCER TREATMENT

Medical Microbiology

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ABSTRACT

Bacterial infections are common in the etiology of human diseases owing to the ubiquity of bacteria. Such infections promote the development of periodontal disease, bacterial pneumonia, typhoid, acute gastroenteritis, and diarrhoea in susceptible hosts. In certain hosts, these illnesses may be treated with antibiotics or antimicrobial therapy. But other hosts might not be able to get rid of the bacteria, which would allow them to linger for a long period and raise the carrier's chance of getting cancer over time. In fact, there are ways to reduce the chance of developing cancer, and this thorough analysis elucidates the intricate connection between bacterial infections and the emergence of many cancer forms. The article also discusses the use of antibiotics in the treatment of cancer, the risks associated with their usage, and methods for reducing antibiotic resistance.It is well known that cancers often develop resistance to conventional therapies, leading to an increased prevalence of drug-resistant forms. This research paper provides an overview of current knowledge regarding mechanisms that contribute to or facilitate drug resistance in anticancer drugs.These mechanisms include drug inactivation, alterations in drug targets, drug efflux, DNA damage repair, inhibition of cell death, and the epithelial-mesenchymal transition.Finally, the association of bacteria in cancer development as well as in cancer therapy on optimal treatment strategies for existing drug-resistant cancers, preventive measures against drug-resistant cancer formation, and potential future development of novel microbe-based therapeutics research directions.

KEYWORDS

Cancer, Bacterial Infection, Antibiotic Resistance, Drug Resistance, Chemotherapy.

INTRODUCTION:

Cancer can affect any region of the body and is a frightening, difficult, and disabling disease [1]. As the second leading cause of death in the US, with almost 2 million new cases and just over 600,000 deaths predicted in 2022, the global cancer epidemic continues to be a public health concern [2]. About 350 people die from lung cancer every day, making it the most common cause of cancer-related mortality [2].

Numerous genetic and epigenetic alterations that impair regular cell development, regulation, and survival lead to cancer.

These alterations are influenced by a broad spectrum of internal and external variables. External factors include diet type, smoking/tobacco usage, radiation, and pathogenic organisms; intrinsic factors include genetic mutations, random mistakes in DNA replication, immunological and inflammatory responses, and other modifiable factors, including ageing [3].

Infectious pathogens such as bacteria and viruses are modifiable causes of cancer, accounting for 20% of all human tumors [4,5]. Even in immuno-competent people, cancer-associated pathogens can display mechanisms such as enduring infection, immune response evasion, chronic inflammation that promotes ongoing cell proliferation, and an elevated risk of oncogenic transformation[6].

The term "human microbiome" refers to the collection of microorganisms that live in the human body, establish intricate biological habitats, and impact human health and disease physiology [7, 8]. The human microbiome can best be defined as a complex assemblage of microorganisms present in many body areas, such as the skin, respiratory system, reproductive tract, gastrointestinal system, and oral cavity and saliva.

The host-bacterial relationships eventually grow into a mutually advantageous partnership [9, 10]. For example, the bacteria that live in the gut receive nourishment from it, which helps with food digestion, nutrient absorption, and the metabolism of indigestible substrates. In addition, this coexistence can support intestinal architecture preservation, immune system modulation, and the avoidance of harmful microbial colonisation [9, 10].

Despite this, the physiological balance in the host cells can be altered by an imbalance in host-bacterial interactions, or dysbiosis. Numerous illnesses, including as inflammatory bowel disease, malnutrition, obesity, diabetes, and cancer, can advance more quickly as a result of this disparity [11, 12].Antibiotics are increasingly being used to treat cancers, often because of their pro-apoptotic, antiproliferative, and antimetastatic potentials [13]. Since infections are also common in cancer patients, it is essential to use antibiotics to prevent and treat bacterial infections [14]. A major limitation of antibiotic use is the causation of dysbiosis due to the elimination of beneficial bacterial groups, such as Lactobacillus and Bifidobacterium, in addition to the pathogenic bacteria [13]. A further limitation is the ability of pathogenic bacteria to evade killing and induce antibiotic resistance [15]. In addition to posing a serious threat to the advancements made in cancer treatment, antibiotic resistance in cancer patients frequently correlates with increased susceptibility to infections that ultimately shorten the patient's survival time [15]. This emphasises the significance of keeping an eye on cancer patients and safeguarding them against antibiotic resistance.

The phenomenon of drug resistance, initially observed in bacteria with antibiotics, is a well-established occurrence where diseases become less responsive to pharmaceutical treatments. This resistance is not limited to specific diseases; it extends to various conditions, including cancer. While certain methods of drug resistance are disease-specific, others, such as drug efflux, are evolutionarily conserved and can be observed both in microbes and drug-resistant cancers in humans. Despite the initial susceptibility of many cancers to chemotherapy, they can gradually develop resistance through various mechanisms like DNA mutations and metabolic changes, leading to drug inhibition and degradation. In addition to conventional cancer treatments like surgery, radiation therapy, chemotherapy, combination therapy, and laser therapy, there is a growing focus on selective therapies that leverage a deeper understanding of tumor biology and molecular genetics to offer promising treatment options [16]. Currently, chemotherapy remains a prominent choice for cancer treatment, despite notable advancements in other modalities. However, a significant challenge in chemotherapy is the emergence of drug resistance, with approximately 90% of treatment failures occurring during cancer invasion and metastasis[17]. This resistance poses a substantial hurdle in cancer therapy, as a considerable proportion of tumor cells develop resistance to the administered drugs. This issue is particularly critical in the field of cancer, and various challenges, including resistance to cytotoxic agents and the toxicity associated with chemotherapy, further complicate cancer treatment. This review

explores the various bacterial infections in cancer patients and its promoting factors in cancer, role of antibiotic and development of drug resistance in anticancer drug, focusing on mechanisms such as drug inactivation, drug target alteration, drug efflux, DNA damage repair, cell death inhibition, and the epithelial-mesenchymal transition (EMT) in response to current treatments. Additionally, the review also discusses the ongoing efforts to address these challenges.

Bacterial Infections during Cancer Treatment

Bacterial infection is one of the most common complications during cancer treatment [18]. Although cancer mortality rates have continued to decline in recent years, bacterial infections remain a significant cause of infection-related mortality in patients[19] . Cancer patients are at a high risk of bacterial infection due to surgical complications, chemotherapy and radiotherapy-related neutropenia, and the use of immunosuppressive drugs during cancer treatment [19,20].Several reports highlight that bacterial infections are prevalent in patients with blood cancers [21,22,23] owing mainly to prolonged neutropenia during treatment [23]. An thorough epidemiological investigation found that patients with haematological cancers had an eight-fold greater incidence of bacterial infections than patients with solid tumours, despite the fact that individuals with solid tumours are similarly susceptible to these infections [24]. A more recent study also revealed that the levels of *Pseudomonas aeruginosa* bloodstream infections were higher in hematological malignancies than in solid tumors [25].Extensive studies have identified a group of six bacterial microbes otherwise classified as the "ESKAPE" pathogens, which are at the forefront of bacterial infection and antibiotic resistance during cancer treatment [26,27]. These organisms include *Acinetobacter baumannii*, *Staphylococcusaureus*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.[26,27].

Researchers at Cairo's National Cancer Institute carried out a comprehensive investigation with the goal of determining how ESKAPE pathogens affected the development of infectious events in young cancer patients. The study found a substantial correlation between the ESKAPE pathogens and increased mortality, longer infection durations, and longer infection times. The study also discovered that the highest fatality rates, at 43% and 30%, respectively, were caused by infections with Pseudomonas aeruginosa and Klebsiella pneumoniae.[28]A similar rigorous study was carried out over a five-year period in hospitalized adults with cancer from 2006 to 2011. All bacteremia episodes in hospitalized cancer patients were included in the investigation. According to the study, Pseudomonas aeruginosa was the most often isolated bacterium, and the ESKAPE pathogens were found to be accountable for 34% of bacteremia episodes in cancer patients [29].Most enterococcal infections in cancer patients are bacteremia caused by *Enterococcus faecalis* [30] Prior exposure to antibiotics and long-term neutropenia are factors that predispose cancer patients to enterococcal infections [30] Urinary tract infections (UTIs), bloodstream infections (BSIs), and endocarditis are common complications for cancer patients exposed to enterococcal infections during therapy [31,32] Reports have also highlighted that *Enterococcus faecalis* often evades treatment owing to its ability to secrete virulent factors and biofilms, and the plasticity of its genome .[33]

Staphylococcus aureus has a significant clinical impact on mortality rate in patients with malignancy [29]. A systematic analysis of bacteremia infections in cancer patients highlights that *Staphylococcus aureus* infections accounts for 1.3% to 12% of all bacteremia cases.[34] Infections caused by *Staphylococcus aureus* often reportedly led to BSIs, skin infections, pneumonia, and endocarditis [35]. Because Staphylococcus aureus may produce enterotoxins and proteases, two virulence factors that impede the host's innate immune response, as well as small colony variations (SCV), the bacteria is of clinical importance [36, 37].In cancer patients, Klebsiella pneumoniae is the most frequent cause of bacteremia, pneumonia, wound infections, abscesses, and urinary tract infections. It is also one of the main causes of sepsis [38]. Because K pneumoniae depends on the existence of an accessory genome for genetic plasticity, the release of virulence factors, and the creation of a thick protective polysaccharide capsule to enable them to evade the host immune system and clearance, the bacteria pose a serious threat to human health.[39, 40] Nosocomial A. baumannii infections, particularly in cancer patients, can be lethal for individuals with weakened immune systems. Acinetobacter baumannii infections result in a much higher death rate in patients—up to 80%. [41] Meningitis, UTIs, skin infections, respiratory tract infections, and BSIs can also cause complications in patients.[41] The pathogenesis of *A. baumannii* infection is severe because the bacterium can adapt to the host environment in several ways, which include the secretion of biofilms (thick polysaccharide capsules) and porins, alongside the release of enzymes and virulence factors. The bacterium also utilizes micronutrient acquisition and protein secretion systems that facilitate its survival even under harsh environmental conditions [42]*Pseudomonas aeruginosa* is an increasingly prevalent opportunistic pathogen that can cause serious and life-threatening nosocomial infections . *P. aeruginosa* has been implicated in causing BSI, respiratory infections, and endocarditis [43]. The bacterium is highly adaptive to the host environment owing to its robust genome and its ability to form biofilms, activate a motile-sessility switch, and secrete secondary metabolites[44].*Enterobacter* spp. can also infect the respiratory tract, surgical wounds, the urinary tract, and the bloodstream of cancer patients [45]. These bacteria facilitate soft-tissue infections, BSIs, and endocarditis. Often, the bacteria population thrives in its host environment through the use of flagellum, the formation of biofilms, and the secretion of endotoxins[46]

Table 1:- List of bacteria and their mechanisms that are associated with various infections in cancer patients

Bacteria	Mechanisms	Disease cause
Pseudomonas aeruginosa	Biofilm formation, secondary metabolites	Blood stream infection, Endocarditis, respiratory infection
Enterobacter spp.	Flagellum, the formation of biofilms, and the secretion of endotoxins	Surgical site infection, urinary tract infection, blood stream infection
Staphylococcus aureus	Enterotoxins and protease enymes	Blood stream infection, soft tissue infection, endocarditis
Klebsiella pneumoniae	Thick protective polysaccharide capsule	Sepsis, pneumoniae, wound infections
Acinetobacter baumannii	Biofilms (thick polysaccharide capsules) and porins, enymes	Blood stream infection, respiratory infection, wound infection

Linkage between bacterial infection and the beginning of cancer

Bacteria and bacterial infections can act as potential carcinogens and tumor promoters [47]. The production of bacterial toxins, enzymes, and oncogenic peptides can all significantly contribute to tumor development by promoting inflammation, interfering with cell cycle control, and disrupting cell signaling pathways [48, 49]. Other studies have also corroborated the fact that microbiota-mediated infection stimulates cancer cell proliferation by targeting host cell DNA, altering the immune system, and promoting epithelial-to-mesenchymal transition [47] . Various examples are as follows

Periodontal disease is a common oral bacterial infection that causes inflammation of the gums (gingivitis) and the tooth-supporting structures (periodontitis) [50]. Periodontal disease can promote long-term and persistent inflammation that can eventually lead to systemic diseases such as cancer of the esophagus [51]. Several types of bacteria have been identified as periodontal pathogens; the most extensively studied are *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, which have been shown to stimulate oral tumor proliferation [52]. These extensively studied organisms in the gums have become the focus of the emerging link between oral bacteria and cancer [53] .

Fusobacterium nucleatum is an anaerobic, gram-negative, disease-causing bacterium in the oral cavity[54]. In addition to this, some researchers have found promising evidence linking periodontitis-related bacteria to other cancers [53, 56]. According to the reports, *F. nucleatum* is prevalent in colorectal adenomas and advanced-stage colorectal cancer (CRC) [57]. It was discovered that *F. nucleatum* causes an inflamm According to studies, F. nucleatum can grow into an opportunistic bacteria that causes gum disease and human cancers when the oral microbiome is dysbiotic [54]. Shorter patient survival periods were shown to be associated with higher levels of F. nucleatum in the tissues of patients with esophageal squamous cancer [54]. As per the latest findings, the pathogenic bacteria responsible for periodontitis might potentially enter the bloodstream through periodontal tissues, dislodge themselves and spread to multiple organs, hence elevating the

likelihood of inflammatory processes in those areas [55]. In addition to this, some researchers have found promising evidence linking periodontitis-related bacteria to other cancers [53, 56]. According to the reports, F. nucleatum is prevalent in colorectal adenomas and advanced-stage colorectal cancer (CRC) [57]. It was discovered that F. nucleatum causes an inflammatory response that enables the persistent proliferation of colorectal cancer cells [57]

Chlamydia trachomatis is a gram-negative bacterium and a prevalent cause of curable sexually-transmitted bacterial infections (STIs) worldwide [58]. The infection presents as urethritis in men and endocervicitis in women [59]. Persistent *Chlamydia* infections have also been identified as a risk factor for developing cervical carcinoma [59], especially in patients with the human papillomavirus (HPV) coinfection [58, 60]. Cervical cancer and C. trachomatis have been linked, according to recent comprehensive meta-analysis studies [61]. The mechanism of the *C. trachomatis* action is proposed as resulting from the dysregulation of DNA damage responses, and the disruption of cell-cycle control, which promotes malignant transformation in infected patients [60].

The association between *C. trachomatis* and cervical cancer is usually seen in the presence of HPV infections [58]. Since HPV infections have long been implicated in the etiology of cervical cancer [62] it is difficult to directly classify the bacterial infection as solely causative, even though it contributes significantly to an increased incidence *Salmonella typhi* is a gram-negative, rod-shaped, flagellated bacterium that is well documented as being responsible for typhoid infections [63,64,65]. Following infection, S. typhi enters the gallbladder and infects vulnerable carriers, who act as a reservoir for the disease's development. This chronic, recurrent infection has also been connected to cancer [64, 66]. The capacity of the pathogen to endure and endure for a prolonged period of time in the gallbladders of patients following infection establishes an environment that is favourable for the promotion of tumours [66]. Additionally, it has been noted that S. typhi generates carcinogenic toxins including nitroso-chemical compounds in addition to typhoid toxins. These substances are essential to the development of cancer [65].. A long-term follow-up study of infected mice discovered the presence of precancerous lesions and dysplasia of the gallbladder, reflecting an association between *Salmonella* infection and gallbladder cancer [67]. Other large-scale studies have also found a link between *S. typhi* infection and gallbladder cancer [65,66,68]

Causes and incidence: Infection by *S. typhi* is usually acquired through the ingestion of food or water contaminated with the feces of a person carrying the organism[63] . *Salmonella typhi* is suspected to be responsible for approximately 22 million cases of typhoid fever, slightly more than 5 million cases of paratyphoid fever, and approximately 200,000 deaths worldwide each year [64]. According to research, some 90% of chronic infection carriers suffer from gallstone infections over time. This association has been described as a significant risk factor for developing gallbladder cancer [67,69,70]

Adaptation strategies for survival and the evasion of treatment: Through the secretion of biofilm, *S. typhi* appears to survive and become well adapted to thrive in the gallbladder. Biofilm formation is a pathological adaptive response that allows the bacteria to aggregate, adhere to surfaces, and develop antimicrobial resistance through the utilization of a thick protective extracellular matrix [64,70]

Mechanism of cancer development after bacterial infection

A number of variables, including host vulnerability, genetic makeup, and favourable environmental conditions, influence the long-term development of carcinogenesis following bacterial infection [71].

Following a successful infection of the host by oral, respiratory, or sexual transmission, the infection might manifest as moderate, acute, or chronic and cause symptoms or no symptoms at all [72]. In order to lessen the illness, antibiotics may now be administered [72]. The microbiome of the infected organ may experience bacterial dysbiosis as a result of the original infection and subsequent antibiotic administration, which in this situation would encourage the growth of pathogenic and opportunistic bacterial species [73, 74, 75]. In certain situations, the administration of antibiotics may entirely remove the infection; in other cases, it may be ineffectual against the bacterium's application of alternate survival strategies, which enable the germs to persist for long periods of time. By dormancy, the release of lethal toxins, the development of protective biofilms, or mutations that result in strains of the bacteria resistant to antibiotics, pathogenic bacteria can endure and remain in the host environment. [76, 77]

Antibiotic usage and antimicrobial resistance in cancer patients:

Antibiotics are secondary metabolites produced by microorganisms, higher animals, and plants, and they have antipathogenic effects that can interfere with the growth of other living cells [78]. Antibiotics are increasingly being used to treat cancers, often because of their pro-apoptotic, antiproliferative, and antimetastatic potentials [78]. Since infections are also common in cancer patients, it is essential to use antibiotics to prevent and treat bacterial infections [79].

A major limitation of antibiotic use is the causation of dysbiosis due to the elimination of beneficial bacterial groups, such as Lactobacillus and Bifidobacterium, in addition to the pathogenic bacteria [80]. A further limitation is the ability of pathogenic bacteria to evade killing and induce antibiotic resistance [81]

It is also worth noting that the microbiome plays a crucial role in the development of antibiotic resistance [82, 83]. The development of resistance, which is frequently brought on by an increase in the number of opportunistic bacteria secreting high quantities of antimicrobial resistance genes, is facilitated by microbiota dysbiosis brought on by antibiotic treatment [84, 85].

Antibiotic resistance in cancer patients is a serious threat to theA progress made in cancer treatment and is often associated with heightened susceptibility to infections that shorten the patient's survival time [81]. It also emphasises the significance of keeping an eye on cancer patients and safeguarding them against antibiotic resistance.

Strategies that could be used to lower cancer patients' antibiotic resistance

Avoiding bacterial infections (prevention is always better than cure): The first stage of bacterial-driven carcinogenesis is usually an initial infection that allows the pathogen to infect the host. Hosts can prevent such infections by being vaccinated and by adopting proper hygiene measures [86]. Another typical approach for cancer patients in neutropenic conditions is antibiotic prophylaxis, which aims to avoid infection and problems connected to infection. Prophylactic quinolone use reportedly decreased hospitalisation, total mortality, fever, and infection rates [81].

The identification and development of new, pathogen-specific antibiotics: The human microbiome can be negatively impacted by the majority of antibiotics, which are intended for broad-spectrum use. This can result in consequences including antibiotic-associated colitis and the quick emergence of antibiotic resistance. The use of narrow-spectrum antibiotics or more focused techniques could help overcome this restriction and offer more resources for growing the pool of antibiotics, which is in danger due to the unavoidable growth in resistance [87].

Optimizing Antibiotic Use (more does not guarantee better): Excessive antibiotic use is a significant driver of resistance [88]. The idea of "antimicrobial stewardship" was created to encourage the prudent use of antibiotics. The process of selecting the most appropriate antibiotic treatment and delivering it for a brief period of time at the lowest feasible dose in order to achieve the greatest possible clinical outcome in battling illness and halting its spread is known as "antimicrobial stewardship" [89]. An infectious disease physician, an infectious disease chemist, and clinical microbiologists who keep an eye on the patient's dosage and reaction make up antimicrobial stewardship teams in clinical settings [81].In a study, the relationship between antibiotic stewardship outcomes and patient mortality was assessed in patients who experienced febrile neutropenia during cancer treatment. According to the study, following antibiotic stewardship guidelines was linked to lower mortality [90].

Chemotherapy and drug resistance in cancer patient:-

Chemotherapy mainly functions by preventing the cancer cells from proliferating and dividing. In addition to growing and dividing far more quickly than normal cells, cancer cells also experience extremely high levels of endogenous stress in their physiological makeup. Consequently, in contrast to other nearby cells, the medications have the ability to kill them faster and more thoroughly. Polyadenosine

diphosphate-ribose polymerase inhibitors, angiogenesis inhibitors, histone deacetylase (HDAC) inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors, p53/mouse double minute 2 homolog (MDM2) inhibitors, hedgehog pathway blockers, tyrosine kinase inhibitors, and proteasome inhibitors are a few of the promising inhibitor therapies that have been used to treat solid cancers. [118,119]. The kind and stage of cancer are the primary factors that influence the choice of chemopreventive medications or a combination of medications. These medications' main goals are to kill malignant cells and lessen the stress brought on by the tumor's growth. Two crucial factors to think about are the treatment's duration and dosage. It has been noted that the drugs are administered at extremely high dosages, which results in a variety of negative effects and damage to other healthy cells. [120]

A significant challenge is the disease's recurrence. It is commonly known that after longer drug exposure, cancer cells develop treatment resistance during recurrence.

Drug resistance in cancer is a complex phenomenon influenced by various factors such as genetic mutations, tumor microenvironment, and tumor heterogeneity. Mechanisms of drug resistance include drug inactivation, reduced drug uptake, increased drug efflux, metabolic effects, inhibition of apoptosis, epithelial-mesenchymal transition, modified membrane transport, and altered gene expression. Genetic and epigenetic alterations also play a role in promoting drug resistance in cancer cells [91,92]. To overcome drug resistance, strategies such as identifying biomarkers for drug response and resistance, developing new targeted drugs, and combination therapies targeting multiple signaling pathways have been proposed. Additionally, bioinformatics approaches and mathematical models are being used to study the evolutionary mechanisms of drug resistance and design effective therapy scheme. Understanding the mechanisms of drug resistance in cancer is crucial for developing novel therapies and improving patient outcomes.

In the context of drug resistance in cancer, both intrinsic and extrinsic factors play crucial roles. Intra-tumor heterogeneity, which occurs at various cancer levels, is primarily attributed to cellular-level factors. This includes natural variations in genetic, epigenetic, transcriptomic, and proteomic properties. Genotypic changes, such as mutations, gene amplifications, deletions, chromosomal rearrangements, transposition of genetic elements, translocations, and alterations in microRNA, contribute to genomic instability and intercellular genetic heterogeneity in cancer. Additionally, epigenetic factors, like miRNA, transcriptomic, and proteomic variations, may arise from genotypic differences, cell cycle stage, stochastic variations, or hierarchical cell organization based on the cancer stem cell theory. These intrinsic factors are responsible for tumor heterogeneity [93,94,95,96]

Extrinsic factors, on the other hand, encompass elements like pH, hypoxia, and paracrine signaling interactions with stromal and other tumor cells [97,98]. These factors alter, increase, or decrease gene products that directly influence the development of drug resistance and contribute to poor prognosis.

The tumor microenvironment also plays a significant role in drug resistance and the recurrence of various cancers. This micro environment involves normal stromal cells, the extracellular matrix, and various soluble factors such as cytokines and growth factors. Communication between tumor cells, stromal cells, and the extracellular matrix contributes to drug resistance. Growth factors and cytokines produced in the tumor microenvironment provide signals for tumor cell growth and survival [99]. Environment-mediated drug resistance (EM-DR) is a comprehensive concept that includes cell adhesion-mediated drug resistance (CAM-DR) and soluble factor-mediated drug resistance (SM-DR). Examples of these soluble factors include VEGF (vascular endothelial growth factor), bFGF (basic fibroblast growth factor), SDF-1 (stromal cell-derived factor-1), IL-6 (interleukin-6), NO (nitric oxide), IL-3 (interleukin-3), G-CSF (granulocyte colony-stimulating factor), M-CSF (macrophage colony-stimulating factor), GM-CSF (granulocyte-macrophage colony-stimulating factor), and TNF super family members such as BAFF (B cell-activating factor of the TNF family) and APRIL (a proliferation-inducing ligand). The interaction of these factors with tumor cells contributes to drug resistance. 8. Benner SE, Wahl GM, Von Hoff DD. Double minute chromosomes and homogeneously staining regions in tumors taken directly from patients versus in human tumor cell lines [99,100,101]. The following mechanism are attributed to drug resistance in cancer cells.

Phytochemical modification of cancer cells through mitochondrial drug resistance mechanism:

Drug-resistant cancer cells may display modifications in mitochondrial metabolism, such as changes in the generation of reactive oxygen species (ROS), which can alter the cell's sensitivity to chemotherapy drugs and contribute to drug resistance. Mitochondrial modifications contribute to treatment resistance in cancer. Phytochemicals target altered mitochondrial pathways to overcome drug resistance [91,92,93] Phytochemicals can modify mitochondrial drug-resistance mechanisms in cancer cells. Phytochemicals increase the potency of chemotherapy drugs and overcome drug resistance. Specific phytochemicals such as curcumin, resveratrol, and quercetin are mentioned as examples. The use of phytochemicals to modify mitochondrial drug-resistance mechanisms in cancer cells. Phytochemicals can enhance the effectiveness of chemotherapy drugs in cancer treatment. Phytochemicals can overcome drug resistance in cancer cells by targeting mitochondrial pathways.

Molecular mechanism to prevent chemotherapy resistance:

Drug resistance in cancer cells can result from various factors, including the tumour microenvironment, immune cells, and cancer stem cells. The exact mechanism of drug resistance is not explicitly mentioned in the paper. Cancer cell resistance is influenced by tumour microenvironment, immune cells, and cancer stem cells. Specialized genomic assessment can assist in choosing effective agents. Understanding drug resistance can lead to new therapeutics. Cancer is a genetic disease with instabilities in protooncogenes and tumour suppressor genes. Heterogeneity of cancer cells influences treatment resistance and failure. Understanding drug resistance mechanisms can lead to the development of more effective and less toxic therapeutics [93]. Specialized genomic assessment can assist in choosing selected agents for cancer treatment.

Mathematical modelling and bioinformatics analyses of drug resistance for cancer treatment:

Mathematical models for drug resistance in cancer therapy, including single-drug resistance and multidrug resistance models explain future cost-effectiveness therapeutics for cancer treatment. The resistance probability and the expected number of drug-resistant tumour cells, which increase with the net reproductive rate of resistant tumour cells. Constrained models, such as logistical growth resistance models, are used to identify realistic treatment strategies for cancer therapy [102]. The bioinformatics methods and machine learning algorithms to study drug resistance focuses on gene co-expression networks and their functions in drug resistance. These methods use multi-omics datasets of cancer cells to predict individual drug response and identify prognostic biomarkers [92,93]. The goal is to develop effective therapy schemes by combining mathematical modelling and bioinformatics approaches. The potential of these approaches in designing treatment strategies for cancer patients.

Basic mechanisms and various modulation strategies involved in cancer drug resistance:

Tumours can develop resistance to currently used drugs, leading to the need for further study and the development of novel therapies. The factors that enable drug resistance, such as inactivation of the drug, reduced drug uptake, increased drug efflux, metabolic effect, inhibition of apoptosis, epithelial-mesenchymal transition, modified membrane transport, and heterogeneity of inherent tumour cells. The genetic and epigenetic alterations that may contribute to drug resistance and fundamental mechanisms of drug reluctance in Leukaemia, ovarian, and breast cancer. The presence of cancer stem cells, which have self-renewal and differentiation capabilities, can also contribute to drug resistance [103]. Other factors such as the tumour microenvironment, immune system evasion, and the presence of drug-resistant clones within the tumour can further enhance drug resistance in cancer. Developing personalized treatment approaches based on the genetic and epigenetic alterations that contribute to drug resistance can improve treatment outcomes. Enhancing drug delivery methods, such as using nanoparticles or targeted drug delivery systems, can improve drug uptake and overcome resistance. Identifying and targeting specific molecular markers or signalling pathways associated with drug resistance can help in the development of targeted therapies. Overcoming the inhibition of apoptosis, a common mechanism of drug

resistance, using apoptosis-inducing agents or inhibitors of anti-apoptotic proteins can sensitize cancer cells to treatment. Understanding and targeting the tumour microenvironment, including factors that promote immune system evasion, can help overcome drug resistance [95,96]. Continuous monitoring of treatment response and adapting treatment strategies accordingly can help manage and overcome drug resistance. paper discusses the interplay between cancer chemoresistance and altered mitochondrial function, focusing on differences in energy metabolism between cancer and normal cells. It explores potential mechanisms of resistance and the development of drugs targeting energy metabolism and nucleotide synthesis. However, it does not specifically mention the mechanism of drug resistance in cancer.

Mitochondrial energy and 1c metabolism on efficacy of anticancer drug resistance:

Cancer chemoresistance and altered mitochondrial function, focusing on differences in energy metabolism between cancer and normal cells. It explores potential mechanisms of resistance and the development of drugs targeting energy metabolism and nucleotide synthesis. However, it does not specifically mention the mechanism of drug resistance in cancer. differences in energy metabolism between cancer and normal cells contribute to chemoresistance. Targeting NAD+, OXPHOS, and 1C metabolism may be a promising approach for anticancer treatment [102, 106]. Mitochondrial energy and 1C metabolism influence anticancer drug efficacy. Differences in energy metabolism between cancer and normal cells contribute to resistance.

The epigenetic perspective of paradigm of drug resistance:

The role of mitophagy, or selective autophagy of mitochondria, in influencing the efficacy of tumour chemotherapy and the degree of drug resistance in cancer cells. However, the precise mechanisms of drug resistance in cancer are not specifically addressed in any of literature search. Mechanisms of mitophagy in chemotherapy resistance are not well understood. Chemotherapy resistance is a common occurrence in cancer treatment. Mitophagy influences tumour chemotherapy efficacy and drug resistance. Acquisition of drug resistance leads to tumour recurrence and poor prognosis [103, 104 105]. Cancer stem cells (CSCs) are considered prime drivers of therapy resistance.

The mitochondrial oncometabolites: a new approach to overcome drug resistance therapy:

The alterations in cellular metabolism and apoptotic programs, including changes in tricarboxylic acid cycle (TCA) enzymes, can lead to drug resistance in cancer. Drug resistance in cancer is a major obstacle in therapy [106,107]. - Targeting oncometabolites production may improve the efficacy of cancer treatment . Targeting Onco metabolites such as 2-hydroxyglutarate, succinate and fumarate, in cancer aggressiveness and drug resistance through pharmacological interventions can potentially improve the efficacy of cancer treatment. Recently a Naphthol derivative, X55 which was identified as targeting cytidine deaminase(CDA)-deficient tumour cells was found to disturb the metabolome of CDA-deficient tumour cells ,worsening the deregulation of many metabolites, including onco-metabolite such as fumarate, succinate and 2 hydroxyglutarate. These finding suggest targeting oncometabolites through specific interventions, such as X55, could hold the promising interventions overcoming drug resistance in cancer improving therapeutic outcomes.

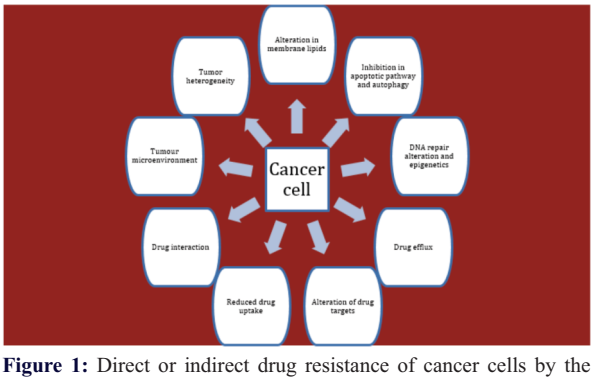

Figure 1: Direct or indirect drug resistance of cancer cells by the mechanism of Alteration in membrane lipids , Inhibition in apoptotic pathways and autophagy , DNA repair alteration and epigenesis , Drug efflux, Alteration of drug targets, Reducing drug uptake , Drug interaction, Tumor microenvironment, Tumor heterogeneity

DISCUSSION:-

Anticancer therapy can potentially exert influence on the development of antibiotic resistance and bacterial infection. The effectiveness of chemotherapy drugs can be compromised by specific bacteria, thus resulting in the emergence of chemotherapy resistance. The presence of antibiotic resistance in bacteria poses a significant threat to the efficacy of cancer therapy, with particular concern surrounding certain pathogens such as *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter spp*. The risk of infection is heightened in cancer patients due to disease-related or therapy-induced immunosuppression, underscoring the critical importance of judicious utilization of anti-infective agents .Bacteria can adapt to the antineoplastic agents used in chemotherapy, leading to an escalation in resistance and the emergence of persistent sub-populations. Neutropenia, which arises because of cancer therapy, can predispose patients to infection, thereby causing treatment delays and an increased level of morbidity and mortality. Employing a targeted approach towards the bacterial nucleotide excision DNA repair mechanism, which bacteria utilize to rectify chemotherapy-induced lesions, offers a promising avenue for the treatment of infections in cancer patients. The adaptation of bacteria to antineoplastic agents used in chemotherapy, resulting in increased resistance to antibiotics. It does not directly address the impact of anticancer therapy on antibiotic resistance and bacterial infection. Bacteria exposed to antineoplastic agents adapt and become resistant to antibiotics. Changes in fatty acid composition and formation of Persister cells observed. Post-chemotherapy infections in cancer patients are caused by bacteria with higher antibiotic resistance. Although actual mechanism of action of anticancer drug resistance is exactly not known but changes in fatty acid composition of cellular membranes and production of Exopolymer substances and formation of aggregates are major contributors of emerging resistance [110]. The DNA replication of bacteria the impact of anticancer chemotherapy on the extension of beta-lactamase spectrum, specifically with KPC-type carbapenems activity towards ceftazidime-avibactam. Anticancer chemotherapy can increase the mutation rates of bacteria. KPC-type carbapenems can extend towards ceftazidime-avibactam. The mechanisms underlying resistance to ceftazidime-avibactam were investigated in a subset of mutants. Upon exposure to certain cytotoxic molecules, the rates of bacterial mutation leading to resistance against ceftazidime-avibactam and rifampicin increased by up to 104-fold. However, no emergence of resistant mutants (with a frequency of <10−10) was observed when meropenem was combined with ceftazidime-avibactam media. In comparison to the parental strains, the ceftazidime-avibactam resistant mutants exhibited heightened susceptibility to meropenem. The bla-KPC genes of these mutants harboured various mutations, deletions, or insertions, particularly in the region responsible for encoding the Ω-loop of the KPC-type carbapenems. The administration of anticancer chemotherapy has the potential to accelerate the mutation rates of bacteria, thereby facilitating the spread of KPC-type carbapenemase towards ceftazidime-avibactam, which is considered one of the last lines of antimicrobial chemotherapy [108,109,110]. As individuals and their caregivers commonly seek health-related information on the Internet, utilizing an online program becomes a viable method for imparting knowledge on infection prevention to patients. The inclusion of Prevent Cancer Infections.org could serve as a valuable resource within the array of tools and materials available to oncology nurses. This online platform has the potential to be a beneficial addition to empower and educate patients.

CONCLUSION:

The link between bacterial infections acquired during cancer treatment and mortality rates is yet to be explored. To better understand the direct link between bacterial infections and cancer development, it will be essential to conduct further long-term follow-up studies on patients with bacterial infections and on the ways in which these infections impact on their risks. Live attenuated strains, toxins, peptides or bacteriocins could be used; alternatively, bacteria could be developed as a drug-delivery system for cancer therapy with the assistance of microbe engineering for tumor targeting. The therapeutic effects of engineered microorganisms in cancer treatment hold immense promise for biomedical applications in targeted cancer therapy. Optimizing Antibiotic Use can minimise the drug resistance in cancer patients and also bacteria and maintain the symbiosis.

Resistance to cancer drugs is a multifaceted phenomenon influenced by various factors such as drug inactivation, alteration of drug targets, drug efflux, DNA damage repair, inhibition of cell death, epithelial-mesenchymal transition (EMT), inherent cell heterogeneity, and epigenetic effects. The prevailing viewpoint suggests that combination therapy represents an optimal approach to combat drug resistance, aiming to prevent its development and enhance treatment efficacy compared to individual drugs alone. This strategy is crucial in addressing the escalating prevalence of drug resistance in cancer [111,112,113]. Cancer progenitor cells, often resistant to drugs, can persist in seemingly remiss patients. These cells have the ability to remain dormant or migrate during metastasis, leading to potential cancer relapse at the original tumor site or in distant organs. The next phase in anticancer therapy development should focus on eliminating these cancer progenitor cells. Additionally, the presence of a small population of drug-resistant cancer cells adds another layer of complexity, contributing to cancer relapse even after apparent remission [114, 115, 116]. Understanding the extent to which cancer progenitor cells and drug-resistant cells contribute to the development of drug resistance is a crucial aspect. Efforts must persist in unraveling the underlying mechanisms of cancer drug resistance and identifying therapies effective against cancers that are no longer responsive to current treatments. Epigenetic drugs are considered potential candidates, as they are believed to sensitize drug-resistant cancer cells to other treatments, and recent studies support this notion [117, 118, 119].Further research in this direction is imperative to enhance our comprehension and treatment of drug-resistant cancers.

Declarations

Ethics approval and consent to participate :- Not applicable

Consent for publication :- Not applicable

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