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Bacterial Interactions Affecting Chemotherapy Effectiveness

Abstract

Chemotherapy resistance is a recurring challenge in cancer treatment, with specific bacteria impairing the effectiveness of certain chemotherapies. This study reviews three bacteria and their impact on chemotherapy drugs: *Mycoplasma* and gemcitabine, *Fusobacterium nucleatum* and oxaliplatin, bacterial β-glucuronase and irinotecan. Bacteria can have wide-ranging effects on cancer treatment; for instance, they may affect drug metabolism, alter toxin conversion, and encourage cancer growth. Whilst the presence of these bacteria was found to have a detrimental effect on the efficacy of chemotherapy treatment, we also consider wider interactions and interdependencies of the microbiota with drug treatments. Some cancer therapies depend on the delicate balance of the microbiome whilst simultaneously disrupting it by their very nature, particularly when antibiotics are introduced. Further research into the complex relationship between bacteria and the tumour micro-environment is needed. Treatments that focus on the immune-oncology microbiome axis or that explore genetic predisposition through the use of biomarkers could also support a more personalised approach.

Introduction

Cancer presents an ongoing health burden globally, with an estimated 19.3 million new cases and 10 million deaths in 2020[1]; it is estimated to be the first or second leading cause of death in 112 countries[2]. Ageing populations contribute to this incidence rising by 47% by 2040[1], with early diagnosis and treatment considered key to improving prognosis and survival.

Chemotherapy has become a well-established cancer treatment since its initial use in the treatment of non-Hodgkin's lymphoma in the 1940s. It is frequently employed alongside other interventions including surgery, radiotherapy, and more recently immunotherapy[3]. Chemotherapy is usually administered intravenously or orally[4], and uses cytotoxic or cytostatic drugs that can interfere with the cell cycle, preventing cell division and proliferation. These can include mitotic inhibitors, topoisomerase inhibitors, alkylating agents, cytotoxic antibiotics, and antimetabolites[5]. Chemotherapy targets non-specifically, so the maximum tolerated dose (MTD) needs to be high enough to be toxic to the cancerous cells without being excessively detrimental to a patient's quality of life[6]. Chemotherapy drug mechanisms depend on various factors such as the nature and location of the tumour. For example, nucleoside analogues such as gemcitabine are taken up through the cell membrane, and they disrupt DNA/RNA synthesis, and either halt the cell division cycle and prevent further cell proliferation (cytostatic), or cause lethal damage leading to apoptosis (cytotoxic)[7].

However, chemotherapy resistance represents an ongoing challenge[8,9] and frequently results in recurrence of the disease and reduced survival rates[10]. Bacterial interactions with chemotherapy drugs have been identified as a potential factor that may reduce the effectiveness of existing treatments[9,11].

Gemcitabine and *Mycoplasma*

Gemcitabine is a commonly prescribed nucleoside analogue antimetabolite chemotherapy prodrug primarily used to treat solid tumours in pancreatic, lung breast, blood, ovarian, bladder and non-small-cell lung cancers[12]. As a hydrophilic drug, it is transported across the cell membrane by nucleoside transporters, phosphorylated by deoxycytidine into its active form as gemcitabine triphosphate, and finally incorporated into DNA and RNA[12]. It cross-primes CD8+ T cells whilst suppressing myeloid-derived suppressor cells (MDSCs), which can otherwise act to downregulate adaptive immune T cell responses[13]. It enhances antigen presentation, downregulating checkpoint molecules and inducing tumour cell apoptosis through various pathways[14]. Although chemotherapy is generally associated with immune suppression, gemcitabine has also been shown to support an adaptive immune response[14,15].

Gemcitabine has been found to be metabolised into an inactive form at solid tumour sites by a long form cytidine deaminase enzyme produced by *Mycoplasma*, a gammaproteobacteria, which renders the treatment less effective or ineffective[5,9,16,17]. Higher *Mycoplasma* infection rates in late-stage cancerous tumour samples compared to benign tissue infections were found in 76% of cancerous pancreatic cells compared to 15% of healthy pancreatic tissue samples[9]; 100% of surgically removed lung tissue was also found to be infected[16]. A higher ratio of *Mycoplasma* infection was found in stage 3-4 gastric cancer samples compared to stage 1-2 gastric cancer samples[7]. This higher occurrence of *Mycoplasma* in tumorous tissue is not yet fully understood[5]. The preferential colonisation of bacteria observed in these studies could arise from the nutrient-rich microenvironment of the tumour due to necrosis[7] or hypoxic anaerobic conditions[18]. Although mycoplasmas usually prefer an aerobic environment, they can also function in the anaerobic environment found in dead or dying tissue. This environmental transition, which is often observed in necrosing tumour tissue, can cause increased production of bacterial toxins and provoke an immune response; the ensuing inflammation may also contribute to chemotherapy resistance[19].

It is also thought that *Mycoplasma* has carcinogenic properties and may contribute to malignant transformations and metastasis[20] through the induction of chromosomal instability, oncogene overexpression, growth factor production, and apoptosis prevention[7]. This raises questions about cause and effect, and whether the bacteria is attracted to the environment of an existing tumour as an opportunistic resident, or if it is a causative agent for the tumour[21].

The bacterial-mediated tumour resistance of gemcitabine is not limited to *Mycoplasma*; thirteen of the twenty-seven types of gammaproteobacteria were found to eradicate the effects of the drug[9]. *Escherichia coli* and *γ-amastigotes* are also associated with gemcitabine resistance[11,17,18]. As *Mycoplasma* is far from being an isolated case, the broader range of bacteria interacting with cancer treatments may have far reaching implications as a subject for further research.

The administration of gemcitabine with antibiotics such as levofloxacin hydrate, cefdinir, ciprofloxacin, and meropenem hydrate has proven useful in improving treatment efficacy by eradicating bacteria[17,22,23].

Oxaliplatin and *Fusobacterium nucleatum*

Oxaliplatin is a platinum analogue of diaminocyclohexane[11], commonly used to treat cancer of the intestines, stomach, pancreas, and oesophagus. It is often administered in combination with other chemotherapy drugs such as cisplatin. Oxaliplatin's anti-tumour activity relies on the production of reactive oxygen species (ROS) in myeloid cells, which is stimulated by the gut microbiota. Gut microbes can prime tumour-infiltrating myeloid cells via the MYD88-dependent pathway for ROS production in response to chemotherapeutic drugs[5,11].

Increased ROS levels are indicative of oxidative stress. This leads to oxaliplatin genotoxicity, inhibiting the synthesis of RNA and DNA. Immunologic reactions are also triggered, with the release of tumour antigens and the translocation of calreticulin phagocytic markers to the cell surface. These promote danger-associated molecule pattern (DAMP) secretions, such as HMGB1 and ATP, which bind to receptors that promote the maturation of death cells and tumour-specific CD8+ T-cells[5,11,14].

Commensal bacteria and microbial metabolites also support oxaliplatin effectiveness by bolstering the immune system. Immunogenic bacteria such as *Bacteroides fragilis* and *Erysipelotrichaceae* work synergistically with antigenicity from epithelial cell apoptosis induced by oxaliplatin to stimulate B cell activation. Butyrate, a microbial metabolite, can enhance oxaliplatin efficacy by activating B cells and cytotoxic CD8+ T cells[5].

Given that an intact microbiome is essential to the functioning of platinum drugs such as oxaliplatin[7], gut microbiota disruption can contribute to chemotherapy resistance or failure. The use of antibiotics can interfere with the microbiome, reducing immune cell mediation of tumour suppressors and pro-inflammatory responses[11,18]. Therefore, care should be taken when prescribing antibiotics and other additional medications alongside oxaliplatin to avoid reducing bacterial diversity, removing beneficial microbes, and having a potential detrimental impact on treatment responses[5,24].

Although the microbiome plays an important role in oxaliplatin efficacy, other types of bacteria can also have a detrimental effect on chemotherapy patients. *Fusobacterium nucleatum* is found to be more prevalent in colorectal cancer patients and is associated with worse prognosis[15] and greater colorectal tumourigenesis. This is due to FadA adhesin and E-cadherin interactions; it induces oxaliplatin chemoresistance by activating toll receptors and switching cell pathways from apoptosis to autophagy, resulting in tumour cell survival[18,25,26]. *F. nucleatum* also contributes to mechanical hyperalgesia, causing sensitivity and pain response in the patient as a dose-limiting complication[26]. These factors all contribute to the limited effectiveness or failure of oxaliplatin as a chemotherapy cancer treatment, and antibiotics are not always a suitable combination treatment due to the impact they can have on microbiome balance[22].

Irinotecan and β-glucuronase

Irinotecan is an antineoplastic semisynthetic water-soluble analogue drug. It is S-phase specific, and inhibits DNA topoisomerase to interfere with DNA replication, transcription, and repair. This causes fatal double-stranded DNA breakage, leading to cell cycle arrest and apoptosis. It is a broad-spectrum chemotherapeutic used mostly in solid tumours, including in brain, gastric, colorectal, pancreatic, lung and ovarian cancers[27].

Although considered an effective chemotherapy drug, irinotecan use is problematic as it often comes with severe side effects[28]. These include delayed diarrhoea (occurring more than 24 hours after administration, generally 5 days), neutropenia (low white blood cell count and impaired immunity), and sometimes an acute cholinergic reaction, resulting from inhibition of acetyl-cholinesterase activity by irinotecan within the first 24 hours of treatment[27,28].

These side effects are attributed to bacterial activity in the gastrointestinal tract. The active form of irinotecan, CPT-11, is administered intravenously and converted by carboxylesterase 2 into the active product SN-38, which subsequently activates anti-neoplastic activity and neutropenia[27]. SN-38 is then detoxified in the liver by UGT1A1 through hepatic glucuronidation to produce SN-38G[29]; however, upon excretion into the gut, bacterial β-glucuronase converts the drug back into the toxic SN-38 metabolite due the deconjugation and reactivation actions of β-glucuronidase[30]. This causes gastric toxicity and intestinal mucosal damage, which in some patients can be severe to life-threatening[5,27,31]. This means drug dosage is often lowered or treatment ceased before the end of treatment, rendering it less effective.

β-glucuronase inhibitors have proven useful alongside irinotecan to limit bacterial β-glucuronidase activity and epithelial damage, as seen in uronic isofagomine derivatives[32]. However, some studies have found that suppressing this activity could produce a secondary SN-38 peak due to enterohepatic recirculation, and the effect on CPT-11 anti-tumour effectiveness is not clear[29]. Ciprofloxacin and other antibiotics have been found to reduce this recycling effect[33].

The microbiota-host-irinotecan axis has identified several supplementary treatments to alleviate the side effects of irinotecan[33]. Benefits of probiotics such as *Bifidobacterium longum*[28,34] and *Lactobacillus rhamnossus*[35] help to regulate the gut microbiota, and faecal microbiota transplantation has also been found effective[28]. Berberine, a plant-based supplement, has been found to strengthen the gut lining, reduce inflammation, and increase production of goblet cells[36].

The ability to metabolise and clear irinotecan can vary ten-fold between patients, which has been partly attributed to polymorphisms in the gene encoding UGT1A1[27]. Genotyping for these mutations may help to detect patients at high risk of irinotecan-induced gastric toxicity as a useful

biomarker for a more personalised treatment[37].

Discussion

Bacteria act as both a friend and a foe in chemotherapy treatment. While balanced bacterial interactions are necessary for immune system drug interactions[7], some microbial interactions may also undermine chemotherapy treatment and thus contribute to chemotherapy resistance or failure. Examples include metabolising drugs before they can be effective, as seen in *Mycoplasma* with gemcitabine[5,9,16]; acting as carcinogens as with *Fusobacterium nucleatum* and oxaliplatin[18,20,25,26]; and producing toxins with side effects so severe that they are intolerable for the patient such as with β-glucuronase with irinotecan[27,28,30,31]. Effects vary even between strains of the same species of bacteria. Notably, the non-enterotoxigenic strain of *Bacteroides fragilis* can enhance efficacy of oxaliplatin while the enterotoxigenic strain of this bacteria promotes colorectal cancer[5].

Higher rates of bacterial infections in cancerous tumours[7,9,16] suggest either a causal relationship as a carcinogen[20,21], an increased attraction of bacteria to the tumour micro-environment[6,11,16,18], or both; there is no consensus as of yet[5].

Much emphasis is placed on the immune-oncology microbiome axis[5] and the bi-directional actions of chemotherapy and the immune system[11]. Effective chemotherapy treatment often relies on aspects of the immune system functioning properly; this is in turn reliant on a balanced microbiome. Chemotherapy treatment can disrupt this balance, contributing to chemotherapy resistance and failure[30]. This is seen for example in the microbiota-host-irinotecan axis[36].

Although antibiotics are useful for treating some cases of bacterial-mediated resistance such as with gemcitabine[23], these drugs are notorious for causing gut dysbiosis and biome imbalance[25,34], so caution must be taken when prescribing these to immunocompromised chemotherapy patients. An emphasis on complementary treatments such as probiotics and faecal microbiota transplants can be a supplementary way to support the immune system as well as the natural balance of the gut, particularly where platinum drugs such as oxaliplatin and irinotecan are being used[28,34,35,36,38].

Understanding an individual's predisposition to bacterial chemotherapy resistance with the use of biomarkers and genotyping for bacterial activity can help medical professionals select the most appropriate drug and dosage for that patient, avoiding unnecessary treatment that is likely to be ineffective or even harmful[31,37]. For example, polymorphisms in gene expression of UGT1A1 may indicate a more severe reaction to irinotecan[27], suggesting that a lower dosage or alternative medication is needed.

In wider research, the importance of bacteria and its role in the immune system is a key part of emerging immunotherapy research as an alternative or complementary form of cancer treatment to chemotherapy[14,27]. Although it has some limitations, such as being more costly as a form of personalised medicine, research outcomes in this area could provide valuable insight into any synergies or crossovers[30].

Conclusion

Bacteria play a significant role in chemotherapy resistance through mechanisms such as tumour growth (*Fusobacterium nucleatum* and *Mycoplasma*), drug metabolism (*Mycoplasma*), and toxin conversion (bacterial β-glucuronase)[19,25,26]. Elucidating the link between bacteria and chemotherapy resistance can help us refine personalised medicine approaches[10]. These include maximizing the effectiveness of chemotherapy treatments by employing biomarkers to measure bacterial activity or by genotyping to identify genetic predisposition[30].

Since bacteria play an essential role in the immune system[5], and with several types of chemotherapy reliant on a healthy balanced microbiome to work effectively[11], there should be an emphasis for future research with some potential synergies with immunotherapy research. Care should be taken with use of antibiotics, as although these may destroy some types of bacteria instrumental in treatment resistance[23], they may destroy other types such as commensal bacterial essential to a healthy microbiota[24,38], so more emphasis on alternatives such as probiotics and faecal microbiota transplants would be of benefit[28,38,34,35,36].

Although there are several factors that may encourage chemotherapy resistance, the role of bacteria is a significant one. Further research is needed to better understand the interplay between the tumour micro-environment and preferential bacterial colonisation, carcinogenic bacterial properties, and the balance between the microbiome and the immune system.

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