Review

A double-edged sword: discussing the value and pitfalls of chemotherapy in cancer treatment, a review of current research

Callista Middleton
Year 3, Medicine, Queen's University Belfast
Email: cmiddleton03@qub.ac.uk

Abstract

As one of the leading causes of death worldwide, research into new therapeutic cancer treatments has been at the forefront of medical study for several years. Yet chemotherapy remains the gold-standard treatment. Thus, its continued implementation and efficacy are important to consider. This review will discuss these aspects further. The author concludes that chemotherapy has both negative and positive value. Prescription is dependent on grade, stage and type of cancer, with some having greater benefit than others. More research is needed to address the issues of developing resistance and senescence, as well as a greater focus on chemotherapeutic use in metastatic disease. This research was accomplished by searching the term 'chemotherapy' on peer-reviewed journal databases for seminal reviews. This led to key terms for further research; 'senescence,' and 'cancer resistance.' Studies were excluded if interventional data was not described in detail. Larger sample sizes were considered before smaller sample studies.

Abbreviations

ATP – Adenosine Triphosphate
BAK – Homologous antagonist/killer protein
BAX – Apoptosis regulator protein
BIM – Bcl-2 interacting mediator of cell death
BCL – B-cell lymphoma
CAF – Cancer associated fibroblasts
CSC – Cancer stem cell
CT – Chemotherapy
AT – Adjuvant chemotherapy
ICT – Induction chemotherapy
NAT – Neoadjuvant chemotherapy
PCT – Palliative chemotherapy
DAMPs – Damage associated molecular pathways
EMT – Epithelial-mesenchymal transition
HMGB1 – High mobility group box 1
IFNy – Interferon gamma
IL-(number) – Interleukin (number)
MHC – Major histocompatibility complex
MMP – matrix metalloproteinase
NF-kB – Nuclear factor-kB
PDGF – Platelet derived growth factor
QOL – Quality of life
ROS – Reactive oxygen species
SASP – senescence-associated secretory phenotype
STAT3 – Signal transducer and activator of transcription 3
TME – Tumour Microenvironment
TNFSF4 – Tumour necrosis factor superfamily 4
VEGF – Vascular endothelial growth factor

Introduction

Cancer involves the growth of abnormal cells within the body. With primary cancer, cells remain within the initial seeded organ creating a tumour. On the contrary, secondary cancer involves cells spreading beyond the initial organ via haematogenous, lymphatic or direct invasion; this process is known as the metastatic cascade. Local invasion allows intravasation of cancer cell aggregates into the circulatory system. After survival and subsequent adherence to the endothelial lining of the vasculature, these cells extravasate forming

micrometastasis which colonise to form macroscopic metastases.[1] This metastasis is limited according to primary tumour environment, summed up by the seed and soil hypothesis: metastasis depends on crosstalk between cancer cells (the 'seeds') and organ tissue tropism (the 'soil').[2]

Once seeded, cancer cells proliferate to become highly heterogenous. Their contents are termed the tumour microenvironment (TME). These include tumour educated macrophages/neutrophils, cancer associated fibroblasts (CAFs) and disordered vasculature, all held within a modified extracellular matrix. These contents allow the TME to produce substances like vascular endothelial growth actor (VEGF), platelet derived growth factor (PDGF), and interleukin-10 (IL-10), which promote angiogenesis and immune suppression, encouraging disease dissemination[3]

Chemotherapy (CT) is a cytotoxic therapy that non-selectively targets proliferating cancer cells. It is prescribed in one of four ways: induction (ICT), neoadjuvant (NAT), adjuvant (AT) and palliative (PCT) CT therapies. The difference between these therapies is timing. ICT describes CT as the primary treatment, used to achieve rapid tumour control. NAT involves shrinking the tumour prior to other treatments, whilst AT involves eliminating left over circulating tumour cells after primary treatment. PCT is used to improve quality of life through symptomatic control – it has no curative intent.

CT is prescribed across a variety of cancer types like lymphoma, breast and rectal.[4] Various drug classes have been synthesised with different biochemical modalities. These include alkylating agents, antimetabolites, antimicrotubule agents and topoisomerase inhibitors (anthracyclines). Each drug class targets a different part of the cell cycle: Alkylating agents destabilise DNA; antimetabolites compete for/substitute key DNA metabolites; and anthracyclines/topoisomerases inhibit enzymes involving DNA uncoiling.[5-6] As such, polychemotherapy is often used to maximise treatment targets. CAPOX is one example which utilises oxaliplatin and capecitabine in the treatment of gastrointestinal cancers.[7] This review will discuss the value of CT as a treatment modality, as well as the issues associated with its use.

Methodology

This research was accomplished by searching on journal databases like PubMed, Elsevier, and Google Scholar using the term 'chemotherapy'. Revision of seminal reviews led to key terms for further research; 'senescence,' and 'cancer resistance.' Only peer-reviewed work published in English was included. Studies were excluded if their focus was outside the scope of the review or if the interventional treatment was not overtly described. All other studies were critically appraised using the 10-step guide produced by Young and Solomon.[8]

Therapy in four forms

Each of the four forms of CT have differing benefits and issues associated with their prescription. One benefit that applies to all four types of therapy is that it is non-selective: able to target different cells of the TME. By causing stress and apoptotic death to the cells, damage-associated molecular patterns (DAMPs) are released in the order of calreticulin, adenosine triphosphate (ATP) and high mobility group box 1 (HMGB1). They interact with corresponding receptors on dendritic cells to allow tumour antigen presentation with subsequent T-cell response. Anthracyclines are particularly effective in allowing calreticulin translocation, but this process of immunogenic cell death can be induced by Bleomycin, Gemcitabine, and Cyclophosphamide.[5,9-10] This is particularly effective for cancers like acute myeloid leukaemia, with 60–85% of adults <60yrs achieving remission status after initial treatment.[11]

However, as dying tumour cells release cell-free chromatin, they also induce apoptosis and inflammation in phenotypically normal cells, leading to undesirable side effects.[12] Tumour lysis syndrome – a life-threatening complication of cancer treatment – is associated with an in-hospital mortality of 21%.[13-14] Other side effects like mucositis and nausea/vomiting can be poorly tolerated, leading to early CT cessation. A study found that of 229 patients receiving CT for early breast cancer, 24% had early cessation of the therapy due to unwanted side effects. A further 18% and 27% had dose reductions and delays respectively, with lethal toxicity occurring in 38%. It is important to note that the retrospective and non-randomised nature of this cohort study limit the integrity of these results.[15] Even so, this highlights how side effects from CT can potentially limit a patient's quality of life (QOL).

Regarding ICT, certain cancers respond particularly well due to their highly proliferative and heterogenous nature. A case review reported that out of 25 patients with choriocarcinoma, 17 had complete recovery after chemotherapy.[16] A phase II trial similarly demonstrated that 85% of 197 patients with acute lymphoblastic leukaemia had complete remission for 29 months on a 5-drug regime containing cyclophosphamide, daunorubicin, vincristine, prednisone and L-asparaginase.[17] Though not beneficial in every malignancy, they are an appropriate primary treatment in highly proliferative and/or system wide cancers such as leukaemia and lymphoma.

When CT is not an appropriate primary treatment, NAT can be used prior to any surgical approaches. This would be indicated in cancers with a solid malignancy, such as breast or lung adenocarcinoma. The BrighTNess randomised control trial (RCT) reported that out of 141 stage II/III triple negative breast cancer patients deemed ineligible for conservation surgery, 75 were deemed eligible after NAT. This equates to 53.2%.[18] Furthermore, a separate study indicated that NAT lowered positive margins from 21.8 to 15.5% in pancreatic head adenocarcinoma ($p<0.0001$). This indicates a promotion of better survival outcomes as positive margins are associated with poorer survival (HR 1.702 $p<0.0001$).[19] As such, NAT is an appropriate treatment when surgical resection is the primary method of care. Other purported rationales for NAT include response assessment to treatment allowing early cessation when deemed ineffective and an improvement in patient survival.[20] One study found that initiation of NAT was associated with a reduction in disease recurrence (HR: 0.73, P=0.003) and mortality (HR: 0.67, P <0.001) when compared with surgery alone. This also included disease-free survival (73.1% vs 64.5%) and 5-year overall survival (79.9% vs 72.6%).[21]

Before the development of NAT, AT was the predominate form of CT, usually prescribed after surgical resection of a tumour to decrease the likelihood of disease recurrence. This has been proven by several different studies. The LACE collaborative group showed an absolute 5-year benefit of 5.4% from the use of Cisplatin AT in non-small cell lung cancer, with benefits dependant on disease staging (1A: HR=1.40, 1B: HR=0.93, II: HR=0.83 etc.)[22] Data analysis from 2000–2009 has similarly shown that cancer mortality has declined by 13.8% with AT drug innovation (8%).[23] An important point to note is that, as the name suggest, AT is used alongside other therapies. It can further be combined with NAT to increase survival, with one study 6.3% increase in survival (p=0.005) of individuals with rectal cancer, compared to those who did not receive both.[24]

What of PCT? A meta-analysis of 11 trials evaluating first-line CT treatment durations in metastatic breast cancer showed statistically significant differences in respect to shorter and longer durations. This was between hazard ratios (0.91, P=0.46) of overall survival and progression free survival (0.64, P= <0.001).[25] The longer treatment lasted, the better the outcome for metastatic disease. Nonetheless, would this simply prolong the inevitable rather than improve QOL? A review of 13 studies by Akhlaghi et al noted that QOL was reduced when PCT was prescribed. Prolonged hospitalisation, invasive ventilation, and death in non-preferred environments were significantly more likely in patients continuing with PCT at end of life. QOL was increased when other needs like mental health, spiritual beliefs and management of symptoms were addressed.[26] One

could argue then that these aspects of care (usually addressed by a specialist palliative care team) are of greater significance to QOL than PCT.

The crux of the issue: developing resistance

One pitfall of CT to consider is treatment resistance. This can occur through the promotion of epithelial-mesenchymal transition (EMT), a process that involves cancerous epithelial cells gaining mesenchymal phenotypes through dissociation with E-cadherin protein. CT can upregulate Snail and Twist transcription factors that lower E-cadherin transcription, promoting further EMT through weakening cell adhesion, thus leading to greater potential for metastasis.[27-28]

Snail and Twist can further affect anti and pro apoptotic protein ratios like BCL-2: BAX, leading to resistance and proliferation via drug target alteration.[29-30] This is particularly detrimental to epithelial-based cancers. One study involving advanced melanoma showed an increase in overall survival rate of 72.9% with a 95% confidence interval when using immunotherapy drug Nivolumab versus 42.1% using CT dacarbazine. Progression free survival was 5.1 months for nivolumab versus 2.2 for dacarbazine with a P value of P<0.001.[31]

The process of anoikis refers to cells which undergo programmed cell death due to detachment from the extracellular matrix. Resistance to this process occurs through overactivation of Src tyrosine kinase (which is upregulated in cancer cells) by reactive oxygen species (ROS). This then leads to BIM protein degradation.[30] BIM forms one of the pro-apoptotic members of the BCL2 family which allow the initiation of apoptosis. When degraded, it can no longer bind to the anti-apoptotic proteins of the same family (BCL2, BCLX etc), causing their levels to become elevated. This inhibits the effector pro-apoptotic proteins (Bax and Bak) from initiating apoptosis. Thus, uncontrolled growth of abnormal cells is promoted.[32] CT promotes anoikis resistance by directly increasing the amount of ROS within the body. Drug classes like the anthracyclines, topoisomerase inhibitors and alkylating agents are all believed to produce the highest number of ROS.[33-34]

ROS can also cause non-specific DNA mutation in non-aberrant healthy cells. Any damage to regulatory genes on these can increase oncogene expression rate, allowing subsequent malignant transformation.[35] Coupled with altered apoptosis, this can lead to an upsurge in metastatic potential.

Senescence

Metastatic potential can be increased by CT through the mobilisation of inflammatory mediators and cancer stem cells (CSCs). Prostaglandin E2 is found in many cancers i.e. colon, lung and breast. When it is secreted by CT-induced dying cells, it promotes CSC proliferation.[5] CSCs have a naturally quiescent nature alongside apoptotic resistance and strong DNA repair abilities. The reliance on cell proliferation by CT means that they are more inherently resistant, able to escape destruction.[33] Having strong damage response mechanisms like nucleotide excision and homologous recombination also allow the potential reversal of drug induced damage; these both would allow reversal of platinum-based drug damage.[30]

CAFs (derived from CSCs), secrete matrix metalloproteinase 3 (MMP) which degrades E-cadherin and promotes EMT.[36] They also limit apoptosis and confer resistance, demonstrated in a study using increased gene tumour necrosis factor superfamily 4 (TNFSF4). This gene had a positive correlation with increased lung adenocarcinoma tumour size after CT with cisplatin. It also had increased expression by the CAFs after CT (n=58 p<0.0001) and was demonstrated to inhibit apoptosis and promote chemoresistance by activating the NF-kb /BCL-XL pathway. It is important to note that research into the role of TNFSF4 in tumour cells is some of the first of its kind. It must be approached with a level of optimistic caution until further peer review.[37]

Furthermore, not every cell is destroyed by CT. Those that remain can instead become senescent. This is a natural consequence of CT due to the induction of DNA double-stranded breaks stopping cell proliferation.[12,35,38] These senescent cells express inflammatory genes that are activated by NF-kB transcription factor allowing the production of several senescence-associated secretory phenotype (SASP) molecules. Examples include IL-1, IL-6, MMP-1 and MMP-3.[36] CT drugs like Cisplatin, 5-Fluorouracil and Mitomycin-C among others induce NF-kB, thus increasing chronic inflammation in the TME.[35] This was demonstrated using doxorubicin. Dermal fibroblasts exposed to 250nM doxorubicin showed a sharp increase in senescence-associated B-galactose indicating increased senescent cell presence, alongside DNA damage from measured 53BP1 foci.[39] Though an initial stopgap for immediate cell proliferation in primary cancer, their accumulation alongside oncogene reprogramming from DNA damage can lead to tumorigenesis through the addition of CSC-like phenotypes.[40] Pharmacological research in other cancer therapies specially aimed at reducing senescence could help mediate chemoresistance.

CT drugs like Paclitaxel and Cyclophosphamide can also cause the production of IL-6, one of the SASP molecules. This cytokine increases M2 macrophages levels which are involved with wound healing and cell proliferation. Furthermore, IL-6 is a potent immunosuppressant in the TME; it inhibits dendritic cells and induces T-regulatory cells (T-reg).[35] One study regarding melanoma interestingly showed that low dose (1–2.5mg per mouse) cyclophosphamide reduced T-reg numbers even with increased IL-6. This however did not allow for greater survival. It also downregulated perforin concentration in cytotoxic T-cells diminishing their function (P<0.05). Most importantly, it promoted the accumulation of inflammatory factors like IL-5 and Interferon gamma (IFNy) (P <0.01) with cyclophosphamide treated mice over untreated same tumour-bearing mice.[40] This increase in inflammation coupled with senescence and the process of immunoediting could explain the similar levels of survival between groups, thus painting CT as a poor adjunct in low dosages.

Combination therapy

What then is immunoediting and what is its significance? Immunoediting is a response of the immune system that involves three phases: elimination, equilibrium and escape. The immune system detects highly immunogenic cancer cells via restricted major histocompatibility complex II (MHC-II) antigen presentation to helper T cells. Cytotoxic T cells then quickly destroy these cancer cells via perforin-1/granzyme B, fas-ligand associated apoptosis and/or IFNy release. Natural Killer T cell activation occurs and protects against further metastasis of antigenically identical cells. However, more weakly immunogenic cells can escape detection and proliferate further, gaining more chemo-resistant and aggressive phenotypes.[10,41] Tumours undergoing this process are described as 'cold,' and difficult to treat with CT. How then can we transform them into immunogenically 'hot' tumours?

Immunotherapy in combination with CT is showing promise amongst current literature. Studies reviewed by Salas-Benito have shown that pembrolizumab (a PD-1 inhibitor) combined with CT increased overall survival (HR 0.49; P <0.001) in non-small cell lung adenocarcinoma and squamous carcinoma (HR 0.64; P <0.001). Early-stage triple negative breast cancer treated with Pembrolizumab and CT also noted a complete response rate of 64.8% versus 51.2% with monotherapy CT, a difference of 13.6% (P<0.001).[42] Even so, immunotherapy has challenges that need addressed. Therapy-related toxicities and 'on target, off tumour' responses leading to treatment failure are just some.[43] Further research into this topic is outside the scope of this review but certainly worth considering.

Final thoughts

The rationale behind CT treatment in cancer is undeniable. With ICT, it has been proven to be relatively effective in highly proliferative

cancers. NAT also helps to improve survival outcomes through lowering positive margins and allowing greater patient inclusion in conservative surgery. AT has been used to help stop the reoccurrence of disease after primary treatment. As new drugs and treatments are discovered, more research is needed to see how AT (and NAT) fit in with this ever-changing oncological landscape. However, metastatic disease still eludes modern science. The actual processes behind how metastasis occur are only now beginning to be understood. Without this basic knowledge, PCT is yet to be used to the fullest. Currently, it remains to improve QOL in end-of-life care, which even then, research suggests is better done via other means – improving mental health etc. PCT is currently not used in a curative fashion but with greater research, one day it could be.

References

1. Fares J, Fares MY, Khachfe HH, Salhab HA, Fares Y. (2020) Molecular principles of metastasis: a hallmark of cancer revisited, Signal transduction and Targeted Therapy, 5(28), [Online]. Available at: https://doi.org/10.1038/s41392-020-0134-x Accessed: 22 January 2024
2. Fidler IJ. (2003) The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited, Nature reviews cancer, 3, pp. 453-458 [Online]. Available at: https://doi.org/10.1038/nrc1098 Accessed: 17 January 2024
3. Anderson NM, Simon MC. (2020) The tumor microenvironment, Cell Press, 30(16), pp. 921-925 [Online]. Available at: https://doi.org/10.1016/j.cub.2020.06.081 Accessed: 27 January 2024
4. Arruebo M, Vilaboa N, Saez-Gutierrez B, Lambea J, Tres A, Valladares M, et al. (2011) Assessment of the evolution of cancer treatment therapies, Cancers, 3(3), pp. 3279-3330 [Online]. Available at: https://doi.org/10.3390/cancers3033279 Accessed: 14 January 2024
5. Tilsed CM, Fisher SA, Nowak AK, Lake RA, Joost Lesterhuis W. (2022) Cancer chemotherapy: insights into cellular and tumor microenvironmental mechanisms of action, Frontiers in Oncology, 12, [Online]. Available at: https://doi.org/10.3389/fonc.2022.960317 Accessed: 16 January 2024
6. Aboud K, Meissner M, Ocen J, Jones R. (2023) Cytotoxic chemotherapy: clinical aspects, Medicine, 51(1), pp. 23-27 [Online]. Available at: https://doi.org/10.1016/j.mpmed.2022.10.005 Accessed: 14 January 2024
7. Cancer Research UK (2024) Cancer drugs A to Z list, Available at: https://www.cancerresearchuk.org/about-cancer/treatment/drugs Accessed: 24 January 2024
8. Young J, Solomon MJ. (2009) How to critically appraise an article, Nature Clinical Practice Gastroenterology & Hepatology, 6(2), pp. 82-91 [Online]. Available at: Accessed: 8 January 2024
9. Hernandez C, Huebener P, Schwabe RF. (2016) Damage-associated molecular patterns in cancer: a double-edged sword, Oncogene, 35, pp. 5931-5941 [Online]. Available at: https://doi.org/10.1038/onc.2016.104 Accessed: 21 January 2024
10. Wang Y-J, Fletcher R, Yu J, Zhang L. (2018) Immunogenic effects of chemotherapy-induced tumor cell death, Genes & Diseases, 5(3), pp. 194-203 [Online]. Available at: https://doi.org/10.1016/j.gendis.2018.05.003 Accessed: 25 January 2024
11. American Cancer society (2019) Cancer treatment & survivorship: Facts & figures 2019-2021, Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survivorship-facts-and-figures-2019-2021.pdf Accessed 30 July 2024
12. Mittra I, Pal K, Pancholi N, Shaikh A, Rane B, Tidke P, et al. (2017) Prevention of chemotherapy toxicity by agents that neutralize or degrade cell-free chromatin, Annals of Oncology, 28(9), pp. 2119-2127 [Online]. Available at: https://doi.org/10.1093/annonc/mdx318 Accessed: 17 January 2024
13. Durani U, Shah ND, Go RS. (2017) In-hospital outcomes of tumor lysis syndrome: a population-based study using the national inpatient sample, The Oncologist, 22(12), pp. 1506-1509 [Online]. Available at: https://doi.org/10.1634/theoncologist.2017-0147 Accessed: 17 January 2024
14. McBride A, Westervelt P. (2012) Recognizing and managing the expanded risk of tumor lysis syndrome in hematologic and solid malignancies, Journal of Hematology & Oncology, 5, [Online]. Available at: https://doi.org/10.1186/1756-8722-5-75 Accessed: 23 February 2024
15. Delgado-Ramos GM, Nasir SS, Wang J, Schwartzberg LS. (2020) Real-world evaluation of effectiveness and tolerance of chemotherapy for early-stage breast cancer in older women, Breast Cancer Research and Treatment, 182, pp. 247-258 [Online]. Available at: https://doi.org/10.1007/s10549-020-05684-5 Accessed: 24 January 2024
16. Yang M, Peng L. (2017) Role of chemotherapy and thrombolysis in treatment of choriocarcinoma accompanied with pulmonary embolism, Medicine, 96(36), [Online]. Available at: https://doi.org/10.1097/MD.0000000000007866 Accessed: 17 January 2024
17. Larson RA, Dodge RK, Burns CP, Lee EJ, Stone RM, Schulman P et al. (1995) A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811, Blood, 85(8), pp. 2025-2037 [Online]. Available at: https://pubmed.ncbi.nlm.nih.gov/7718875/ Accessed: 23 February 2024
18. Golshan M, Loibl S, Wong SM, Houber JB, O'Shaughnessy J, Ruho HS et al. (2020) Breast conservation after neoadjuvant chemotherapy for triple-negative breast cancer, JAMA Surgery, 155(3), [Online]. Available at: https://doi.org/10.1001/jamasurg.2019.5410 Accessed: 23 January 2024
19. Greco SH, August DA, Shah MM, Chen C, Moore DF, Masanam M et al. (2021) Neoadjuvant therapy is associated with lower margin positivity rates after Pancreaticoduodenectomy in T1 and T2 pancreatic head cancers: an analysis of the National Cancer Database, Surgery Open Science, 3, pp. 22-28 [Online]. Available at: https://doi.org/10.1016/j.sopen.2020.12.001 Accessed: 20 January 2024
20. Masood S. (2016) Neoadjuvant chemotherapy in breast cancers, Women's Health, 12(5), pp. 480-491 [Online]. Available at: https://doi.org/10.1177/1745505716677139 Accessed: 23 February 2024
21. Aliseda A, Arrendondo J, Sánchez-Justicia C, Alvarellos A, Rodríguez A, Matos I et al. (2024) Survival and safety after neoadjuvant chemotherapy or upfront surgery for locally advanced colon cancer: meta-analysis, British Journal of Surgery, 111(2), pp. znae021 [Online]. Available at: https://doi.org/10.1093/bjs/znae021 Accessed: 27 November 2024
22. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepaerd FA, Stephens RJ et al. (2008) Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group, Journal of clinical oncology, 26(21), pp.3552-3559 [Online]. Available at: https://doi.org/10.1200/JCO.2007.13.9030 Accessed: 27 November 2024
23. Lichtenberg FR. (2014) Has medical innovation reduced cancer mortality?, CESifo Economic Studies, 60(1), pp. 135-177 [Online]. Available at: https://doi.org/10.1093/cesifo/ift014 Accessed: 22 January 2024
24. Polanco PM, Mokdad AA, Zhu H, Choti MA, Heurta S. (2018) Association of adjuvant chemotherapy with overall survival in patients with rectal cancer and pathologic complete response following neoadjuvant chemotherapy and resection, JAMA Oncology, 4(7), pp. 938-943 [Online]. Available at: https://doi.org/10.1001/jamaoncol.2018.0231 Accessed: 25 January 2024
25. Gennari A, Stockler M, Puntoni M, Sormani M, Nanni O, Amadori D et al. (2011) Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials, Journal of Clinical Oncology, 29, [Online]. Available at: https://doi.org/10.1200/JCO.2010.31.5374 Accessed: 26 January 2024
26. Akhlaghi E, Lehto RH, Torabikha M, Nia HS, Taheri A, Zaboli E et al. (2020) Chemotherapy use and quality of life in cancer patients at the end of life: an integrative review, Health Qual Life Outcomes, 18, [Online]. Available at: https://doi.org/10.1186/s12955-020-01580-0 Accessed: 26 September 2024
27. Su J-X, Li S-J, Zhou X-F, Zhang Z-J, Yan Y, Liu S-L, Qi Q. (2023) Chemotherapy-induced metastasis: molecular mechanisms and clinical therapies, Acta Pharmacologica sinica, 4, pp. 1725-1736 [Online]. Available at: https://doi.org/10.1038/s41401-023-01093-8 Accessed: 24 February 2024
28. Dart A. (2023) EMT in chemoresistance, Nature Reviews Cancer, 23, [Online]. Available at: https://doi.org/10.1038/s41568-023-00581-7 Accessed: 25 January 2024
29. Taddei ML, Giannoni E, Fiaschi T, Chiarugi P. (2011) Anoikis: an emerging hallmark in health and diseases, The Journal of Pathology, 226(2), pp. 380-393 [Online]. Available at: https://doi.org/10.1002/path.3000 Accessed: 21 January 2024
30. Hasan S, Taha R, Omri HE. (2018) Current opinions on chemoresistance: an overview, Bioinformation, 14(2), pp. 80-85 [Online]. Available at: https://doi.org/10.6026/97320630014080 Accessed: 25 February 2024
31. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L et al. (2015) Nivolumab in previously untreated melanoma without BRAF mutation, The New England Journal of Medicine, 372(4), pp. 320-330 [Online]. Available at: https://doi.org/10.1056/NEJMoa1412082 Accessed: 22 February 2024
32. Koenig MN, Naik E, Rohrbeck L, Herold MJ, Trouson E, Bouillet P et al. (2014) Pro-apoptotic BIM is an essential initiator of physiological endothelial cell death independent of regulation by FOXO3, Cell Death & Differentiation, 21, pp. 1687-1695 [Online]. Available at: https://doi.org/10.1038/cdd.2014.90 Accessed: 27 January 2024
33. Yang H, Villani RH, Wang H, Simpson MJ, Roberts MS, Tang M et al. (2018) The role of cellular reactive oxygen species in cancer chemotherapy, Journal of Experimental & Clinical Cancer Research, 37, [Online]. Available at: https://doi.org/10.1186/s13046-018-0909-x Accessed: 24 January 2024
34. de Freitas Saito R, Rangel MC, Chandler M, Beasock D, Afonin KA, Chammas R. (2023) Cancer therapy-induced inflammation and its consequences, in Ribeiro de Araujo D, Carneiro-Ramos M. (ed.) Biotechnology Applied to Inflammatory Diseases. Interdisciplinary Biotechnological Advances. Singapore: Springer [Online]. Available at: https://doi.org/10.1007/978-981-19-8342-9_4 Accessed: 15 January 2024
35. Behranvand N, Nasri F, Emameh RZ, Khani P, Hosseini A, Garssen J et al. (2021) Chemotherapy: a double-edged sword in cancer treatment, Cancer Immunology, Immunotherapy, 71, pp. 507-526 [Online]. Available at: https://doi.org/10.1007/s00262-021-03013-3 Accessed: 22 January 2024

36. Feng B, Wu J, Shen B, Jiang F, Feng J. (2022) Cancer-associated fibroblasts and resistance to anticancer therapies: status, mechanisms, and countermeasures, Cancer Cell International, 22, [Online]. Available at: https://doi.org/10.1186/s12935-022-02599-7 Accessed: 16 January 2024
37. Li Y, Chen Y, Miao L, Wang Y, Yu M, Yan X et al. (2021) Stress-induced upregulation of TNFSF4 in cancer-associated fibroblast facilitates chemoresistance of lung adenocarcinoma through inhibiting apoptosis of tumor cells', Cancer Letters, 497, pp. 212-220 [Online]. Available at: https://doi.org/10.1016/j.canlet.2020.10.032 Accessed: 16 January 2024
38. Prasanna PG, Citrin DE, Hildesheim J, Ahmed MM, Venkatachalam S, Riscuta G et al. (2021) Therapy-induced senescence: opportunities to improve anticancer therapy, Journal of the National Cancer Institute, 113(10), pp. 1285-1298 [Online]. Available at: https://doi.org/10.1093/jnci/djab064 Accessed: 20 January 2024
39. Demaria M, O'Leary MN, Chang J, Shao L, Liu S, Alimirah F et al. (2017) Cellular senescence promotes adverse effects of chemotherapy and cancer relapse, Cancer Discovery, 7(2), pp. 165-176 [Online]. Available at: https://doi.org/10.1158/2159-8290.CD-16-0241 Accessed: 22 February 2024
40. Sevko A, Sade-Feldman M, Kanterman J, Michels T, Falk CS, Umansky L et al. (2013) Cyclophosphamide promotes chronic inflammation–dependent immunosuppression and prevents antitumor response in melanoma, Journal of Investigative Dermatology, 133(6), pp. 1610-1619 [Online]. Available at: https://doi.org/10.1038/jid.2012.444 Accessed: 17 January 2024
41. Watson LJ. (2023) Immune response, Available at: https://geekymedics.com/immune-response/ Accessed: 21 February 2024
42. Sala-Benito D, Pérez-Gracia JL, Ponz-Sarvisé M, Rodriguez-Ruiz ME, Martínez-Forero I, Castañón E et al. (2021) Paradigms on immunotherapy combinations with chemotherapy, Cancer Discovery, 11(6), pp. 1353-1367 [Online]. Available at: https://doi.org/10.1158/2159-8290.CD-20-1312 Accessed: 27 September 2024
43. Tang L, Huang Z, Mei H, Hu Y. (2023) Immunotherapy in hematological malignancies: achievements, challenges and future prospects, Signal transduction and targeted therapy, 8, [Online]. Available at: https://doi.org/10.1038/s41392-023-01521-5 (Accessed: 27 September 2024

Callista Middleton

Hi there! My name is Callista, and I am a third-year graduate medical student at Queen's University Belfast. I am currently interested in the fields of infectious medicine, pathology and cardiology. Specifically, I have a passion for parasitology and how such organisms can affect the body on both a macro and microscopic level. Outside of medicine, I am a keen Dungeons and Dragons (DnD) player, as well as an avid foodie.