Chemotherapy- Type, Side Effects and Resistance

Siti Fatimah Ibharm[1] and Norjihada Izzah Ismail [1,2*]

[1]School of Biomedical Engineering and Health Sciences, Universiti Teknologi Malaysia, 81310 UTM Skudai, Johor, Malaysia

[2*]Medical Devices and Technology Centre, Universiti Teknologi Malaysia, 81310 UTM Skudai, Johor, Malaysia

Corresponding author email: norjihada@ utm.my
Accepted December 2020, available online 30 December 2020

ABSTRACT

Chemotherapy is one of the most common cancer treatment therapies used to treat various types of cancer through regular interval exposure to drugs. There are different types of chemotherapeutic drugs such as alkylating agents, antimetabolites, anti-tumor antibiotics, topoisomerase inhibitors II, and mitotic inhibitors that can be used to inhibit cancer cells from growing further and spread to other parts of the body. Cancer cells tend to grow and proliferate very fast in supportive environment whereas chemotherapy drugs exhibit certain level of ability to eliminate these fast-growing cells. However, these drugs may be disseminated throughout the body and cause damage to healthy cells. Indeed, chemotherapy may induce adverse effects in multiple organ systems and the issues with toxicity commonly restrict the usefulness of chemotherapeutic drugs. Despite its widespread use and acceptance, it has been associated with a number of side effects including nausea, discomfort, diarrhea and hair loss. Unpleasant side effects of current treatment drugs following chemotherapy has led to more research directed on identifying potential uses of natural products such as from plants (plant-derived based alternative therapies) for use in cancer treatment. Drug resistance is another challenge in chemotherapy. This mini review provides some information on types of chemotherapy, their side effects and resistance following treatment regimes.
Keywords: PID, Couple tank system, Control system, LABVIEW software, Lab kit.

1. Introduction

Cancer is categorized as one of the major causes of death worldwide and more than 12 million individuals were diagnosed with cancer annually [1-3]. Since decades, doctors and scientists across entire world have been working on various researches for the remedy to combat cancer cells, but the accomplishment in fighting these abnormal cells still showed limited outcome [3]. Chemotherapy is a fundamental component that used drugs or chemicals to destroy dividing cancer cells and inhibit them from growing further and till now it is still the major therapeutic approach after surgical resection of tumor cells [4,5]. Unfortunately, the nature of chemotherapy could also harm healthy cells and tissues, delivered inadequate dosage to the cancerous regions that will lead to adverse reactions [6,7]. Likewise, previous study found that patients who receive low dosage of chemotherapy have less survival rate and increased the incidence of death [3,8]. Listed below in Table 1 are several categories of chemotherapy agents that are used against different types of cancer cells [9,10].

Table 1. Overview of chemotherapeutic agents classes [9,10]

Drug class	Examples	Indications
Alkylating agents	• Chlorambucil • Cyclophosphamide • Busulfan	• Hodgkin's lymphoma • Solid tumors (breast, ovarian and lung) • Myeloablation prior to hematopoietic stem cell transplant
Antimetabolites	• 5-fluorouracil (5-FU) • 6-mercaptopurine (6-MP) • Gemcitabine	• Breast cancer • Pancreatic cancer • Acute lymphoblastic leukemia

Anti-tumor antibiotics	• Doxorubicin • Dactinomycin • Daunorubicin • Bleomycin	• Solid tumors • Leukemia • Squamous cell carcinomas of head and neck
Topoisomerase inhibitors II	• Etoposide • Teniposide	• Testicular cancer • Leukemia
Mitotic inhibitors	• Docetaxel • Eribulin • Paclitaxel • Vinblastine	• Ovarian cancer • Breast cancer • Gastric cancer • Kaposi sarcoma

Alkylating agents were among the first chemotherapeutic drugs developed in the early 1940's. This type of drugs acted directly on DNA which triggered cross-linking of DNA strands, abnormal base pairing that could inhibit DNA replication, hence preventing division of tumor cells [11]. Besides, alkylating agents kill the cell in multiple phase of cell cycle and usually labeled as cell cycle phase nonspecific [12]. Next, antimetabolites agents interfere with DNA synthesis and thus could modify the enzymes needed for cellular uptake and protein synthesis [13]. Indeed, antimetabolites agents are considered cell cycle specific due to their antitumor performance that may destroy actively multiplying cells [12]. Mitotic inhibitors, on the other hand, originated from plant alkaloids and play roles in preventing cells from keep dividing to form new cells [12]. Nonetheless, these inhibitors can destroy cells in all phases of cycle by preventing enzymes from making proteins that really crucial for cellular reproduction [14,15].

Besides, topoisomerase inhibitors are chemotherapeutic agents that block the actions of topoisomerase enzymes (topoisomerase I and II) and thus could interrupt DNA replication [13]. According to Thorn et al. [16], doxorubicin is one of the topoisomerase II inhibitors that works by intercalating DNA that can block topoisomerase-II-mediated DNA repair along with production of reactive oxygen species that eventually destroy membranes and protein [3,12]. Although it is used in many types of cancers, this drug was unsafe due to its cardiotoxic effects that could lead to heart failure [16]. Besides, antitumor antibiotics which comprise of natural products from anthracyclines, mitomycins, and actinomycins work by binding with DNA and preventing RNA synthesis, in which a key step in protein synthesis. This category of drugs are considered cell cycle non-specific as these antibiotics work throughout cell cycle [13].

2. Chemotherapy side effects and drug resistance

According to WHO classification, chemotherapy is interconnected with several side effects that include immediate signs of toxicity and late signs of chronic toxicity starting from mild, moderate, severe or life threatening [17,18]. Previous literature by Schirrmacher [19] mentioned that the immediate effects of chemotherapy can be noticed from the skin and hair, bone marrow and blood, kidney. All important organs of the body such as heart, lungs and brain could also be affected. Additionally, the severe and life threatening neurotoxicity level can cause paralysis, ataxia, coma, spasm whereas the chronic effects of chemotherapy treatment include carcinogenicity, drug resistance, and infertility. Aslam et al. [20] revealed that the highest reported side effects were weakness (95%), fatigue (90%), nausea (77%), hair loss (76%) and vomiting (75%). There were also less occurring side effects which include mouth sores, diarrhea, dry mouth, abdominal cramps, memory impairment and numbness. Indeed, nausea and vomiting are among the most common side effects [21].

Other than that, it was reported that 90% failures in chemotherapy during the invasion and metastasis of cancers are due to the drug resistance [22]. Drug resistance in cancer cells results in decrease drug activity which enhance tumor insensitivity to the initial treatment or increase tumor resistance during or after treatment [23,24]. Listed below in Table 2 are frequently used anticancer drugs with identified side effects.

Table 2. Commonly used anticancer drugs with identified side effects.

Cancer type(s)	Type/ classes of chemotheraphy drug	Side effects	Reference(s)
Non-Hodgkin's lymphoma, multiple myeloma, breast cancers	Doxorubicin	• Heart damage • Soles of the feet, swelling and pain. • Skin eruptions on the palms of the hand	Motlagh et al. [3]

Ovary, head, neck and lung cancers	Carboplatin (Paraplatin)	• Decrease in blood cell counts • Hair loss (reversible) • Nause, vomiting • Confusion • Diarrhea	Crawford [25]
Ovary, pancreas, lung and breast cancerous	Gemcitabine	• Bleeding gums • Diarrhea • Loss of appetite • Chest pain • Joint pain	Motlagh et al. [3]
Breast, ovary and lung cancers	Paclitaxel (Taxol)	• Allergic reaction • Thin or brittle hair • Joint pain • Decrease in blood cell counts • Nausea and vomiting • Numbness or tingling in the fingers or toes	Crawford [25]
Lymphoma cancer	Dacarbazine	• Myelosuppression • Vomiting • Perivascular irritation	Chun et al. [26]
Metastatic breast cancer	Docetaxel with Capecitabine (DX)	• Nausea, discomfort, asthenia • Neutropenia • Diarhea	Miles et al. [27]

Drug resistance in chemotherapy involves several mechanisms including decrease in drug activation, alteration of drug targets, drug efflux, enhance DNA damage repair, cell death inhibition, epithelial-mesenchymal transition (EMT) and metastasis as well as cancer cell heterogeneity [22,28]. Cancer cells develop resistance to the treatments by decreasing drug activation through mutation or overexpression in the proteins and enzymes of the activation pathways such as cytochrome P450 (CYP) system and glutathione-S-transferase (GST) superfamily [28]. Overexpression of GST leads to increase detoxification of anticancer drugs thus limits drug damaging activity on cancer cells [22,29]. Alterations of drug targets arise following mutations or modifications of expression levels of the targets. As a result, cancer cells with mutated drug target do not respond properly to the drug, thus alter the purpose of mentioned drug and eventually lead to drug resistance [22].

Drug efflux, on the other hand, refers to the mechanism of pumping the anticancer drugs out of cells to reduce drug accumulation [30]. Cancer cells cause efflux of drug through two types of drug resistance-associated membrane proteins (DRAMPs) known as ATP-binding cassette (ABC) transporter and solute carrier transporter. ABC transporter pumps the hydrophobic drugs out of tumor cells while solute carrier transporter increases the level of chemoresistance. Consequently, these membrane transporter proteins decrease the efficacy of drugs into tumor cells and affect the cellular uptake of hydrophilic anticancer agents [31].

3. Conclusion

It can be concluded that chemotherapeutic drugs can be used in targeting different stages of cell cycle, disrupting DNA and RNA synthesis, preventing DNA damage repair and so forth. However, some of these expected outcomes may not be attained due to the several mechanisms of drug resistance that promote survival of cancer cells following chemotherapy. Despite of these side effects and drug resistance, chemotherapy remains methods of choice for cancer treatments.

Acknowledgement

Authors thank Universiti Teknologi Malaysia and Ministry of Higher Education Malaysia for providing the financial support (Research University Grant 15J38 and 17J40)

4. References

[1] Torpy, J. M., Lynm, C., and Glass, R. M. (2010). JAMA patient page. Cancer: the basics. JAMA, Volume 303(11), (2010), pp. 1108. Doi: 10.1001/jama.303.11.1108

[2] Chan, H. K., and Ismail, S. Side effects of chemotherapy among cancer patients in a Malaysian general hospital: Experiences, perceptions and informational needs from clinical pharmacists. Asian Pacific Journal of Cancer Prevention, Volume 15(13), (2014), pp. 5305–5309. https://doi.org/10.7314/APJCP.2014.15.13.5305

[3] Motlagh, N. S. H., Parvin, P., Ghasemi, F., Atyabi, F., Jelvani, S., and Abolhosseini, S. Laser induced fluorescence spectroscopy of chemo-drugs as biocompatible fluorophores : irinotecan ,gemcitabine and navelbine. Laser Physics Letters, Volume 13(7), (2016), pp. 75604. Doi: https://doi.org/10.1088/1612-2011/13/7/075604

[4] Morris, P., and Lassman, A. Optimizing chemotherapy and radiotherapy for anaplastic glioma. Nat Rev Clin Oncol, Volume 7, (2010), pp. 428–430. https://doi.org/10.1038/nrclinonc.2010.98

[5] Huang, C. Y., Ju, D. T., Chang, C. F., Muralidhar Reddy, P., and Velmurugan, B. K. A review on the effects of current chemotherapy drugs and natural agents in treating non-small cell lung cancer. BioMedicine (France), Volume 7(4), (2017), pp. 12–23. Doi: https://doi.org/10.1051/bmdcn/2017070423

[6] Bai, J., Liu, Y., and Jiang, X. Multifunctional PEG-GO/CuS nanocomposites for near infrared chemo-photothermal therapy. Biomaterials, Volume 35(22), (2014), pp. 5805–13. Doi: https://doi.org/10.1016/j.biomaterials.2014.04.008

[7] Pearce, A., Haas, M., Viney, R., Pearson, S. A., Haywood, P., Brown, C., and Ward, R. Incidence and severity of self-reported chemotherapy side effects in routine care: A prospective cohort study. PLoS ONE, Volume 12(10), (2017), pp. 1–12. https://doi.org/10.1371/journal.pone.0184360

[8] Kuo, S. H., Lien, H. C., You, S. L., Lu, Y. S., Lin, C. H. Chen, T. Z., and Huang, C.S. Dose variation and regimen modification of adjuvant chemotherapy in daily practice affect survival of stage I-II and operable stage III Taiwanese breast cancer patients. The Breast, 17(6), (2008), pp. 646-653. Doi: https://doi.org/10.1016/j.breast.2008.05.006

[9] Katzung, B., and Trevor, A. Basic and Clinical Pharmacology, (2014). McGraw-Hill Education.

[10] Trevor, A. J., Katzung, B. G., and Knuidering-Hall, M. Katzung & Trevor's Pharmacology Examination and Board Review,11th Edition, (2015). McGraw Hill Professional.

[11] Florea, A. M., and Büsselberg, D. Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. Cancers (Basel), Volume 3, (2011), pp. 351–1371.

[12] Abotaleb, M., Kubatka, P., Caprnda, M., Varghese, E., Zolakova, B., Zubor, P., and Büsselberg, D. Chemotherapeutic agents for the treatment of metastatic breast cancer: An update. Biomedicine and Pharmacotherapy, Volume 101, (2018), pp. 458–477. https://doi.org/10.1016/j.biopha.2018.02.108

[13] Gustafson, D. L., and Page, R. L. Cancer Chemotherapy. Withrow and MacEwen's Small Animal Clinical Oncology: Fifth Edition (Fifth Edition), (2012). Elsevier Inc. https://doi.org/10.1016/B978-1-4377-2362-5.00011-6

[14] Checchi, P. M., Nettles, J. H., Zhou, J., Snyder, J. P., and Joshi, H. C. Microtubule-interacting drugs for cancer treatment. Trends Pharmacol. Sci, Volume 24, (2003), pp. 361–365.

[15] Mukhtar, E., Adhami, V. M., and Mukhtar, H. Targeting microtubules by natural agents for cancer therapy. Mol. Cancer Ther, Volume 8, (2014), pp. 275–285

[16] Thorn, C. F., Oshiro, C., Marsh, S., Hernandez-Boussard, T., McLeod, H., Klein, T. E., and Altman, R. B. Doxorubicin pathways: pharmacodynamics and adverse effects. Pharmacogenet. Genomics, Volume 21, (2012), pp. 440–446

[17] Schirrmacher, V. Quo Vadis Cancer Therapy? Fascinating discoveries of the last 60 years. Lambert Academic Publishing, (2017), pp. 1–353.

[18] Koeppen, B. M., and Stanton, B. A. Berne and Levy Physiology. 7th edition. Elsevier, Amsterdam. (2018), pp.880.

[19] Schirrmacher V. From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment (Review). International journal of oncology, Volume 54(2), (2019), pp. 407–419. https://doi.org/10.3892/ijo.2018.4661

[20] Aslam, M. S., Naveed, S., Ahmad, A., Abbas, Z., Gull, I., and Athar, M. A. Side Effects of Chemotherapy in Cancer Patients and Evaluation of Patients Opinion about Starvation Based Differential Chemotherapy. Journal of Cancer Therapy, Volume 5, (2014), pp. 817-822. Doi: 10.4236/jct.2014.58089.

[21] Sugerman, D. T. Chemotherapy. JAMA, Volume 310(2), (2013), pp. 218. Doi:10.1001/jama.2013.5525

[22] Mansoori, B., Mohammadi, A., Davudian, S., Shirjang, S., and Baradaran, B. The different mechanisms of cancer drug resistance: a brief review. Adv Pharm Bull, Volume 7(3), (2017), pp. 339–348

[23] Hurley, L. H. DNA and its associated processes as targets for cancer therapy. Nat Rev Cancer, Volume 2, (2002), pp. 188-200.

[24] Khan, H., Ullah, H., Martorell, M., Valdes, S. E., Belwal, T., Tejada, S., and Kamal, M. A. Flavonoids nanoparticles in cancer: Treatment, prevention and clinical prospects. Seminars in Cancer Biology, (2019), pp. 0–1

[25] Crawford, S. Is it time for a new paradigm for systemic cancer treatment . Lessons from a century of cancer chemotherapy. Volume 4(6), (2013), pp.1–18

[26] Chun, R., Garrett, L. D., and Vail, D. M. Cancer Chemotherapy. Withrow & MacEwen's Small Animal Clinical Oncology (Fourth Edition, Vol. c), (2007), Elsevier Inc

[27] Miles, D., Vukelja, S., Moiseyenko, V., Cervantes, G., Mauriac, L., Van, H. G., Liu, W. Y, Ayoub, J. P., and O'Shaughnessy, J. A. Survival benefit with capecitabine/docetaxel versus docetaxel alone: analysis of therapy in a randomized phase III trial. Clinical Breast Cancer, Volume 5 (4), (2004), pp. 273–278

[28] Housman, G., Byler, S., Heerboth, S., Lapinska, K., Longacre, M., Snyder, N., and Sarkar, S. Drug resistance in cancer: an overview. Cancers. Volume 6(3), (2014), pp. 1769–1792

[29] Allocati N, Masulli M, Di Ilio C, and Federici L. Glutathione transferases: substrates, inihibitors and pro-drugs in cancer and neurodegenerative diseases. Oncogenesis, Volume 7(1), (2018), pp. 8

[30] Xue, X, and Liang, X. J. Overcoming drug efflux-based multidrug resistance in cancer with nanotechnology. Chinese Journal of Cancer, Volume 31(2), (2012), pp. 100–109

[31] Choi, C. H. ABC transporters as multidrug resistance mechanisms and the development of chemosensitizers for their reversal. Cancer cell international, Volume 5(1), (2005), pp.30