

A Review of the Use of Targeted Therapy for Cancer Treatment

Abstract

One of the serious health problems of today's societies is cancer, which many efforts have been made to deal with. Despite the many studies conducted in the field of cancer treatment and the provision of various treatments in this field, cancer cells show resistance to the offered treatment strategies (even chemotherapy) and leave the offered treatments without results. Therefore, scientists have tried (especially in the last two decades) to use smart ways to successfully fight cancer. Among the appropriate solutions presented in recent years is targeting the weak points of neoplastic cells and using them to make drugs. The use of this method makes it more likely that cancer cells will not have a chance to fight. Targeted cancer treatment usually includes two different approaches: the first approach is to use special drugs to target the weak points of cancer cells, and the second approach is to deliver the drug directly to the abnormal cells and avoid more collateral damage to the patients. The main goal of these studies is to provide personalized treatments to each patient based on the underlying cause of his illness, which will bring medical science into the field of person-centered medicine. In this review article, using reliable and new sources, the goals that are used for this targeted treatment are introduced along with the logic of their selection and the drugs obtained from them.

Keywords: Targeted therapy, Cancer treatment, Resistance, Chemotherapy, Targeted cancer treatment

Introduction

For years, cancer has affected many people and is the second leading cause of death worldwide after cardiovascular diseases.^[1] Cancer is a very complex genetic, epigenetic, and environmental disease and has many variations in tissue, tumor, and cellular levels, which can lead to inappropriate treatments.^[2, 3] By disrupting the amazing order of body cells, cancer cells ignore the rules governing cell division and do their work.

The speed of tumor progression depends on the individual's biological, immunological, genetic, and environmental backgrounds. The complexity of cancer increases with the discovery of various gene sequences involved in it, especially tumor suppressor genes and molecular pathways.^[4, 5] However, evidence has shown that a significant part of cancer predisposing factors cannot be attributed to changes in protein-coding sequences. As an example, the identification of a large number of long non-coding RNAs or lncRNAs with a length of more than 200 base pairs in humans has revealed the role of these molecules in

cancer pathology and their role in tumorigenesis.^[6]

It is believed that mutation is a long and multi-step process that is created by the accumulation of mutations in various loci of the genome. Therefore, extensive studies in the field of specific diagnosis and appropriate treatment are vital. However, cancer cells are also able to use the body's intelligent mechanisms to survive and fight against therapeutic agents.^[4, 7-9]

This is why scientists are trying to propose the best option for the treatment regimen of each patient by accurately identifying the mutations involved in the development of each cancer so that with this approach, the side effects of chemotherapy can be prevented as much as possible and the treatment efficiency can be improved. The important point in this is that these drugs should be able to target primary mutations or "drivers" in the cancer process, instead of "passenger" mutations that occur in many types of cancer,^[9-11] to do this, two different strategies have been suggested: 1- Examining the genome of each person's cancer cells, especially in the initial stages and before metastasis, to find the mutations

Yeuan Ting Lee¹, Yi Jer Tan¹, Chern Ein Oon^{1*}

¹Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia, Pulau Pinang, Malaysia.

Address for correspondence:

Chern Ein Oon,
Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia, Pulau Pinang, Malaysia.
E-mail: chern.oon@usm.my

Access this article online

Website: www.ccij-online.org

DOI: [10.51847/thpfMsiACR](https://doi.org/10.51847/thpfMsiACR)

Quick Response Code:



How to cite this article: Lee YT, Tan YJ, Oon CE. A Review of the Use of Targeted Therapy for Cancer Treatment. Clin Cancer Investig J. 2023;12(6):33-7. <https://doi.org/10.51847/thpfMsiACR>

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: Support_reprints@ccij-online.org

© 2023 Clinical Cancer Investigation Journal

responsible for causing the disease. In this case, the best drug can be selected to target the defective pathway. 2- Finding solutions that can deliver chemotherapy drugs with the highest concentration to the cancer mass.^[12]

The main goals of targeted cancer therapy

Cell signaling routes

One of the things that plays a great role in the process of carcinogenesis is the disruption of the order of cell signaling pathways that leads to excessive cell proliferation or prevents cell proliferation from stopping at the necessary time.

The Epidermal Growth Factor Receptor (EGFR) pathway is one of the most important tyrosine kinase pathways, which, as its name suggests, stimulates cell growth and proliferation. In a study that was conducted on a special group of patients with non-small cell lung cancer (Non-Small Cell Lung Carcinoma, NSCLC),^[13] the second active loop of 47 genes out of 58 human tyrosine kinase genes was investigated. It was found that among them in the EGFR protein, a range of genetic changes; including deletions in exon 19 and certain missense mutations in the activator loop (LS58R) and the P protein loop (G7195). In this study, the study group was people who showed a very good response to AstraZeneca (Gefitinib Jressa 21839). It was determined by the investigations that this drug inhibits the phosphorylation of the downstream pathways of the epithelial growth factor, so it can have the best results for people who have this primary mutation in their tumor cells. The discovery of this problem caused this drug to be prescribed only for a specific target group, because its administration to other people, except for side effects, will not affect their tumor growth in the long term.

However, in another study, it was shown that several patients in the target group of this drug also showed relative resistance to Gefitinib after some time, which is most likely caused by the presence and activity of cancer stem cells in the heterogeneous mass.^[14] In this case, a monoclonal antibody named DMC-C225 Erbitux (Cenuximab) was used, which has a more targeted mechanism and by connecting to the second domain of this receptor, it causes its internalization and stops the messaging. Another important point in this study was that this mutation is much more common in the Japanese population than in the American population, which can raise questions about ethnic influences on the development of different cancers.

For the RAS pathway, which is located downstream of EGFR, due to the existence of different mutations, inhibition strategies, and different targeted drugs have been designed.^[15] For example, the RAS protein requires a post-transcription modification (PT) for its normal function, during which a farnesyl group is attached to it. Several drugs have been designed to inhibit this PTC, which are known as Farnesyl Transferase Inhibitors (FTIS).

Some drugs such as the ISIS family have no noticeable effect on their own despite inhibiting the farnesyl group connection.

This has several reasons; among other things, the inhibition of this process can replace the connection of the geranyl-geranyl-geranyl group to the corresponding proteins, and the functional changes created in this case will not be completely predictable. Therefore, only finding the target path for it is not enough to design the drug, one must be able to predict its function in the very complex context of the body system. Another aspect of RAS pathway proteins that can be controlled by drugs is their kinase function.^[16]

Angiogenesis

Another aspect of tumors, which extensive efforts are underway to control, is their angiogenesis, which involves multiple pathways. The vascular Endothelial Growth Factor (VEGF) pathway is one of the most important pathways involved in angiogenesis, which has two important receptors named FLT1 and FLK1. VEGF protein is targeted by a monoclonal antibody, which is created Beracizumab drug (Genentech, Avastin). This drug is the first targeted therapy to inhibit angiogenesis that has been approved by the FDA. Also, 9006-43-Bay and 011248-SU are being investigated for kidney cancer. Another therapeutic method used to inhibit this pathway is small-molecule antagonists, including SU5416 and SU6668. These small molecules competitively occupy the tyrosine kinase position of the receptors of this pathway and deactivate the pathway. A new generation of these molecules called SU011248 has also been designed that can inhibit multiple receptors. Therefore, it is used for patients who are in the advanced stages of the disease and have multiple tumors.^[17]

Another protein that is very important in the path of angiogenesis is called hypoxia-inducible factor (1-Hypoxia-Inducible Factor, HF), which is activated in the condition of reduced oxygen in cells and causes angiogenesis and maintains cell survival. Drugs designed to inhibit this protein are generally small-molecule antagonists.^[18] The mechanism of most of them is gradually being introduced because many of them induce inhibition of HIF-1 α through the inhibition of other molecules.^[19] Even topoisomerase inhibitors with microtubule polymerization inhibitors can inhibit the function of HIF-1 α . Therefore, their mechanism is not considered targeted and specific. On the other hand, HIF-1 α requires HSP-90 for its stability. Therefore, by targeting this molecule, the angiogenesis pathway can be controlled.^[12]

Another alternative pathway leading to HIF-1 α inhibition is through mTOR inhibition. The Mammalian Target of Rapamycin is activated by mTOR through the signaling pathway of PI3-kinase and AKT kinase, stimulating the translation of mRNA related to HIF-1 α protein.^[19-21] Therefore, these drugs are also designed against this protein.^[22] It should be noted that drugs such as PT2399 for targeting 2-HF have recently been proposed and are undergoing pre-clinical stages.^[23]

Genome stability

Disruption of the ability to maintain the stability of the genome is one of the important factors underlying the development of

neoplastic cells. Considering this weakness of cancer cells, one of the most promising treatment solutions is to use drugs that cause damage to the genome in cells where DNA repair pathways are damaged.^[24] In this case, the drug only causes the death of abnormal cells, and other healthy cells of the person's body can deal with this environmental stress due to their ability to repair their genome. Among the main drugs used for this purpose are alkylating agents. Another group of these drugs includes platinum-containing substances. It should be noted that scientists have proposed combined treatments in a more intelligent way, in which the regenerative pathways of cancer cells are first inhibited with solutions, and then genomic damage is caused by using the mentioned drugs. This approach makes alkylating or platinum drugs usable in a wider range of people. Although, unfortunately, the possibility of side effects of chemotherapy also increases.^[24, 25]

Targeted transfer methods

Medicine, as mentioned earlier, is one of the types of targeted cancer treatment, inventing and using methods that can directly transfer the drug to the cancer cells and by preventing the drug from reaching the healthy cells of the person, the side effects of chemical drugs Minimize treatment. Of course, these treatments can face difficulties in practice. However, there are three different strategies for this task: The first and most widely used method is the use of antibodies, in which the antibodies are designed in such a way that they identify the specific surface marker of cancer cells and bind to it. In this case, based on the characteristics of these antibodies, drugs can be divided into two main categories. In the first category, monoclonal antibodies act directly as drugs, in which case they are called functional antibodies. These molecules are inactive in the bloodstream and only after binding to the cells, do they show lethal properties to some extent. Although the number of these drugs is, limited, they are usually used in combination with other chemotherapy drugs or at the same time as radiation therapy. Even in some cases, radioisotopes are attached to them to increase the lethality. In the second case, antibodies are used as a carrier that passively carries the drug in the bloodstream and delivers it to the target cancer cell. In this case, binding to special receptors causes their internalization and transports the drug into the cell. Drugs are usually attached to amino groups of lysines (Lysines) in FC regions or constant regions of carrier antibodies.^[26]

The number of drug molecules should be carefully adjusted in such a way that it does not hurt the solubilization property of the antibody and does not have cytotoxicity or excessive effects. In the field of designing this type of drug, the results of the initial efforts were known as first-generation drugs. Antibodies of these drugs are mouse or human-mouse chimera, and the drug's binding agent is needed for them to separate from the acidic properties of endosomes with proteasome properties of proteasomes. Although this generation of drugs, due to their allogeneic antibodies, partially causes an immune response in the patient and limits the repetition of the treatment. For this reason, in subsequent efforts, second-generation drugs with fully human antibodies and disulfide linkers were designed and used. Methotrexate and doxorubicin

are the most important drugs of the first generation Toxoids are second-generation drugs.^[26]

The second targeted method is designed based on this strategy that rapidly growing cell masses have many vessels that do not have a complete structure due to the speed of synthesis and are so-called leaky. Therefore, if the drugs are present in the bloodstream for the necessary time, these cells absorb the drug faster and more than the normal cells of the body. To escape from the reticuloendothelial system and keep the drug in the bloodstream longer, nanoparticles with a hydrophilic surface and an approximate diameter of 100 m are used. If the surface of these nanoparticles is covered with antigens that target specific antigens on the surface of cancer cells, an efficient and targeted system for drug delivery to cancer cells will be provided. This transfer system is even used to transfer genes into cancer cells. For example, lipid-based cationic nanoparticles (Lipid-based cationic nanoparticles) were used to deliver the mutated Raf gene to mouse tumors, and the mutant protein produced was able to inhibit several signaling pathways and reduce tumor growth. This method of gene transfer has been used for various types of cancers and is still being increasingly investigated.^[27-29]

One of the latest solutions that has attracted the attention of scientists is the use of non-slowing RNAs to inhibit or regulate signaling pathways. One of the most important members of this group is miRNAs. MicroRNAs are a group of short RNAs with an approximate length of 19-21 nucleotides, which are effective on the stability of mRNAs and are responsible for regulating the expression level of many genes. These sequences, some of which have specific promoters and some are located within the intronic or exonic sequences of other genes, after passing through several precursor stages and with the help of enzymes, become mature and active. Then each mRNA binds to the target mRNAs and based on the degree of matching with the corresponding sequence, they lead to the suppression of the expression of the target gene product.^[30]

It should be noted that many other mechanisms have been proposed for the functioning of miRNAs, some of which even include increasing the expression of genes because of binding to miRNAs.^[31, 32] According to the set of mentioned cases, the use of miRNAs as medicine requires a lot of precision and control. However, researchers have introduced several sequences as a treatment approach that, if they can appear effective in clinical trials, can be considered very successful hopes in the fight against cancer. In these studies, miRNAs are proposed both as molecular targets for drugs and as drug inhibitors to suppress other genes. For example, increasing the expression of miR-193a is one of the molecular targets to help AML patients who have mutations in the C- gene.^[33] On the other hand, the miR 29 family has been introduced as one of the best drug sequences to suppress the progression of AMIL in mouse models.^[34]

Another group of non-slowing RNAs, which are among new therapeutic hopes, is called small interfering RNA (SIRNA). These sequences are generally synthetic and approximately

21-23 nucleotides in length, which play a role similar to miRNA. According to The process mentioned, siRNAs can prevent the expression of target genes, which have been used to treat cancers.^[35]

Conclusion

Cancer is perhaps one of the most complex human problems in the field of health, which imposes a lot of financial and emotional costs on societies every year. Due to the intelligent function of cancer cells to deal with therapeutic strategies, the need for better drug design cannot be ignored. One of the most suitable solutions is the design of chemotherapy drugs based on the weak points of cancer cells, which makes the treatment for each patient individually and specifically designed to have the highest efficiency with minimal side effects. In this context, targeting cell signaling pathways including EGFR and RAS, angiogenesis pathway and genome repair pathway have brought successful results so far. Another method under investigation is the use of targeted and efficient delivery methods for drugs, which nanoparticles, miRNAs, and siRNAs have been successful in this field so far.

Acknowledgments

None.

Conflict of interest

None.

Financial support

None.

Ethics statement

None.

References

- Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A systematic analysis for the global burden of disease study. *JAMA Oncol.* 2017;3(4):524-48.
- Rutka JT, Taylor M, Mainprize T, Langlois A, Ivanchuk S, Mondal S, et al. Molecular biology and neurosurgery in the third millennium. *Neurosurgery.* 2000;46(5):1034-51. doi:10.1097/00006123-200005000-00002
- Keung W, Cheung YF. Human pluripotent stem cells for modeling of anticancer therapy-induced cardiotoxicity and cardioprotective drug discovery. *Front Pharmacol.* 2021;12:650039. doi:10.3389/fphar.2021.650039
- Noori-Dalooi MR, Zekri A. Genetic instability and centrosome abnormality in cancer. *Med Sci* 2014;24(3):125-35.
- Song S, Jung S, Kwon M. Expanding roles of centrosome abnormalities in cancers. *BMB Rep.* 2023;56(4):216-24. doi:10.5483/BMBRep.2023-0025
- Noori-Dalooi MR, Eshaghkhani Y. lncRNAs roles in cancer occurrence. *Med Sci.* 2015;25(3):163-82.
- Belete TM. The current status of gene therapy for the treatment of cancer. *Biol: Targets Ther.* 2021;15. doi:10.2147/BTT.S302095
- Zhang J, Zhang H, Xu X, Wang M, Yu Z. Comparative genomic hybridization analysis of invasive ductal breast carcinomas in the Chinese population. *Oncol Lett.* 2015;10(4):2100-6.
- Fares J, Fares MY, Khachfe HH, Salhab HA, Fares Y. Molecular principles of metastasis: A hallmark of cancer revisited. *Signal Transduct Target Ther.* 2020;5(1):28. doi:10.1038/s41392-020-0134-x
- Willis RE. Targeted cancer therapy: Vital oncogenes and a new molecular genetic paradigm for cancer initiation progression and treatment. *Int J Mol Sci.* 2016;17(9):1552.
- Lin X, Xiang X, Hao L, Wang T, Lai Y, Abudoureyimu M, et al. The role of Aurora-A in human cancers and future therapeutics. *Am J Cancer Res.* 2020;10(9):2705-29.
- Sawyers C. Targeted cancer therapy. *Nature.* 2004;432(7015):294-7.
- Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. *Science.* 2004;304(5676):1497-500.
- Seshacharyulu P, Ponnusamy MP, Haridas D, Jain M, Ganti AK, Batra SK. Targeting the EGFR signaling pathway in cancer therapy. *Expert Opin Ther Targets.* 2012;16(1):15-31.
- De Luca A, Maiello MR, D'Alessio A, Pergameno M, Normanno N. The RAS/RAF/MEK/ERK and the PI3K/AKT signaling pathways: Role in cancer pathogenesis and implications for therapeutic approaches. *Expert Opin Ther Targets.* 2012;16 Suppl 2:S17-27.
- Downward J. Targeting RAS signaling pathways in cancer therapy. *Nat Rev Cancer.* 2003;3(1):11-22.
- Gschwind A, Fischer OM, Ullrich A. The discovery of receptor tyrosine kinases: targets for cancer therapy. *Nat Rev Cancer.* 2004;4(5):361-70.
- Semenza GL. Targeting HIF-1 for cancer therapy. *Nat Rev Cancer.* 2003;3(10):721-32.
- Ghosh R, Samanta P, Sarkar R, Biswas S, Saha P, Hajra S, et al. Targeting HIF-1 α by natural and synthetic compounds: A promising approach for anti-cancer therapeutics development. *Molecules.* 2022;27(16):5192. doi:10.3390/molecules27165192
- Hudson CC, Liu M, Chiang GG, Otterness DM, Loomis DC, Kaper F, et al. Regulation of hypoxia-inducible factor 1 α expression and function by the mammalian target of rapamycin. *Mol Cell Biol.* 2002;22(20):7004-14.
- Di Conza G, Trusso Cafarello S, Loroch S, Mennerich D, Deschoemaeker S, Di Matteo M, et al. The mTOR and PP2A pathways regulate PHD2 phosphorylation to fine-tune HIF1 α levels and colorectal cancer cell survival under hypoxia. *Cell Rep.* 2017;18(7):1699-712.
- Wick W, Gorlia T, Bady P, Platten M, van den Bent MJ, Taphoorn MJ, et al. Phase II study of radiotherapy and temsirolimus versus radiochemotherapy with temozolomide in patients with newly diagnosed glioblastoma without mgmt promoter hypermethylation (EORTC 26082). *Clin Cancer Res.* 2016;22(19):4797-806.
- Cho H, Du X, Rizzi JP, Liberzon E, Chakraborty AA, Gao W, et al. On-target efficacy of a HIF-2 α antagonist in preclinical kidney cancer models. *Nature.* 2016;539(7627):107-11.
- Helleday T, Petermann E, Lundin C, Hodgson B, Sharma RA. DNA repair pathways as targets for cancer therapy. *Nat Rev Cancer.* 2008;8(3):193-204.
- Thomas ML, Coyle KM, Sultan M, Vaghar-Kashani A, Marcato P. Chemoresistance in cancer stem cells and strategies to overcome resistance. *Chemotherapy.* 2014;3(125):2.
- Chari RV. Targeted cancer therapy: Conferring specificity to cytotoxic drugs. *Acc Chem Res.* 2008;41(1):98-107.
- Kim TH, Jin H, Kim HW, Cho MH, Cho CS. Mannosylated chitosan nanoparticle-based cytokine gene therapy suppressed cancer growth in BALB/c mice bearing CT-26 carcinoma cells. *Mol Cancer Ther.* 2006;5(7):1723-32.
- Lee HY, Mohammed KA, Nasreen N. Nanoparticle-based targeted gene therapy for lung cancer. *Am J Cancer Res.* 2016;6(5):1118-34.
- Wang K, Kievit FM, Zhang M. Nanoparticles for cancer gene therapy: Recent advances, challenges, and strategies. *Pharmacol Res.* 2016;114:56-66.
- Noori-Dalooi MR, Vand Rajabpour F. Roles of miRNAs in gene expression regulation, apoptosis, diagnosis and treatment of cancer. *Med Sci.* 2011;21(3):151-61.
- Eulalio A, Huntzinger E, Izaurralde E. Getting to the root of miRNA-mediated gene silencing. *Cell.* 2008;132(1):9-14.
- Lee S, Vasudevan S. Post-transcriptional stimulation of gene expression by microRNAs. *Adv Exp Med Biol.* 2013;768:97-126.
- Gao XN, Lin J, Li YH, Gao L, Wang XR, Wang W, et al. MicroRNA-193a represses c-kit expression and functions as a methylation-silenced

- tumor suppressor in acute myeloid leukemia. *Oncogene*. 2011;30(31):3416-28.
34. Gong JN, Yu J, Lin HS, Zhang XH, Yin XL, Xiao Z, et al. The role, mechanism, and potentially therapeutic application of microRNA-29 family in acute myeloid leukemia. *Cell Death Differ*. 2014;21(1):100-12.
35. Morris KV. siRNA-mediated transcriptional gene silencing: The potential mechanism and a possible role in the histone code. *Cell Mol Life Sci*. 2005;62(24):3057-66.