Analyzing Two Approaches to Treating Cancer: Chemotherapy Versus Targeted Therapy

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Abstract

Targeted therapy has significantly advanced the field of oncology and improved patient outcomes in recent years. However, many hurdles remain in replacing the more toxic chemotherapy that is still in use. These two therapies differ in multiple aspects, including the mechanism of action. Unlike chemotherapy which targets all cells, targeted therapy only targets cancer cells. Beyond the biology that each therapy targets, there are several factors, including socioeconomic factors, that determine the need and availability of these treatments. In this review article, we investigate each of these factors and their differing impacts on types of cancers, patients, and regions. Moreover, we share our perspectives and insights on essential changes on the medical and social fronts that can widen the reach of targeted therapy to patients around the world.

Keywords: chemotherapy, targeted therapy, cancer, socioeconomic factors

Introduction

Chemotherapy is a form of cancer treatment that uses drugs to kill cancerous cells or prevent them from growing. Some of the most common types of chemotherapy are alkylating agents, plant alkaloids, and antimetabolites. An alkylating agent is a form of chemotherapy that attaches an alkyl group to the guanine base of DNA (1). Before being used in chemotherapy, alkylating agents were used as sulfur mustard (“mustard gas”) and in weapons during World War I. Nitrogen mustards were the first alkylating agents used medically as well as the first modern form of chemotherapy (2). Today, there exists 5 types of alkylating agents: nitrogen mustards, nitroureas, alkyl sulfonates, triazines, and ethylenimines. Some types of nitrogen mustards include bendamustine, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, and melphalan; some types of are nitrosoureases are carmustine, lomustine, and streptozocin; one alkyl sulfonate is busulfan; some triazines are dacarbazine and temozolomide; and some ethylenimines are altretamine and thiotepa (3). The article, “The Nitrogen Mustards”, states that when nitrogen mustards are combined with small-molecule targeted agents and monoclonal antibodies, the overall response in breast cancer and melanoma is 100% and 85%, respectively (14). Plant alkaloids are small organic molecules that contain nitrogen, usually in a ring (6). Alkaloid-containing plants have been used as early as 2000 BC in Mesopotamia and today, they’re categorized into 5 main types: alkaloids, protoalkaloids, polyamine alkaloids, peptide and cyclopeptide alkaloids, and pseudoalkaloids. Some types of true alkaloids include atropine, nicotine, and morphine; some types of protoalkaloids are ephedrine and mescaline; some polyamine alkaloids are coniine and caffeine; some peptide and cyclopeptide alkaloids are ergotamine and amatoxin; and some pseudoalkaloids are colchicine and quinine (7). The article, “Tetrandrine: a review of its anticancer potentials, clinical settings, pharmacokinetics, and drug delivery systems”, states that in breast cancer xenograft mouse models, tetrandrine significantly reduces tumor volume and weight (15). An antimetabolite is a substance that inhibits the use of a metabolite (10). Some types of antimetabolites include 5-fluorouracil (5-FU), 6-mercaptopurine (6-MP), capecitabine (Xeloda®), cytarabine (Ara-C®), gemcitabine (Gemzar®), and pemetrexed (Alimta®) (11).

There are several aspects to chemotherapy: the way it's synthesized or produced, the mechanism of action, the delivery mechanism into cells, and the efficacy or results of this treatment in cancer patients. Alkylating agents are produced through amino acid nitrosation. This involves the reactions of alpha-, beta-, and gamma-amino acids. These reactions produce amino acids with an -NH(2) group, namely alpha-lactones, beta-lactones, and gamma-lactones, which serve as alkylating agents against cancer (4). Alkylating agents cease tumor growth by crosslinking guanine nucleobases in DNA double-helix strands, directly attacking DNA. This prevents the strands from uncoiling and separating, halting cell division (5). Many alkaloids are present in raw plants in the form of either salts or organic acids. The way they're extracted is by processing the raw material with an alkaline solution and extracting the alkaloid bases with organic solvents such as 1,2-dichloroethane, chloroform, diethyl ether, or benzene. Then, the impurities are dissolved by weak acids which convert the alkaloid bases into salts that are washed away with water. The process is repeated until the desired purity is achieved (8). Plant alkaloids act as a defense system in living organisms and play a vital role in chemotherapy (9). Antimetabolites impair DNA by incorporating chemically altered nucleotides or depleting the supply of deoxynucleotides needed for DNA replication and cell proliferation. They're considered the first generation of chemotherapy and work by inhibiting the action of an enzyme that's crucial to an organism's metabolic processes (12). They're often used in cancer treatments in that they interfere with DNA production, cell division, and tumor growth. They're most commonly used to treat leukemia, breast, ovary, and intestinal cancer (13).

Targeted therapy is a form of cancer treatment that blocks the proliferation of cancer cells by interfering with specific molecules that cause abnormal cell growth. There are four types of targeted therapy: angiogenesis inhibitors, monoclonal antibodies, proteasome inhibitors, and signal transduction inhibitors. Angiogenesis inhibitors are substances that inhibit angiogenesis, the growth of new blood vessels. Certain types of angiogenesis are shown to be linked to the formation of malignant tumors and the expression of several pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGR) which these inhibitors aim to stop (16). Angiogenesis inhibitors can be classified as either endogenous or exogenous. Endogenous angiogenesis inhibitors originate from an organism and are a normal part of the body's control and exogenous angiogenesis inhibitors are obtained from external sources such as pharmaceutical drugs (17). Monoclonal antibodies, also called mAb or moAb, are antibodies that are produced by cloning a unique type of white blood cell and creating a cell line. The first use of mAbs was documented in the early 1900s by an immunologist named Paul Ehrlich. More recently in 2018, James P. Allison and Tasuku Honjo received the Nobel Peace Prize in Physiology or Medicine for discovering cancer therapy by the inhibition of negative immune regulation, using mAbs that prevent inhibitory linkages (20). The mAbs approved by the FDA for cancer are Alemtuzumab, Bevacizumab, Cetuximab, Dostarlimab, Gemtuzumab ozogamicin, Ipilimumab, Nivolumab, Ofatumumab, Panitumumab, Pembrolizumab, Ranibizumab, Rituximab, and Trastuzumab (21). Proteosome inhibitors are drugs that block the actions of proteosomes, cellular complexes that break down proteins (24). Only three have been approved for treating multiple myeloma: Bortezomib, Carfilzomib, and Ixazomib. Bortezomib, or Velcade, was approved by the FDA in 2003 and it was the first proteasome inhibitor approved in the US. Its boron atom binds to the catalytic site of the 26S proteasome. Carfilzomib, or Kyprolis, was approved for relapsed and refractory multiple myeloma in 2012 and it binds to and inhibits the chymotrypsin-like activity of the 20S proteasome. Ixazomib, or Ninlaro, was approved in 2015 for use in combination with lenalidomide and dexamethasone for the

treatment of multiple myeloma and it's the first orally-available proteasome inhibitor (25). Signal transduction inhibitors are drugs that block signals passed from one molecule to another inside a cell. Blocking these signals can affect many cellular functions such as mitosis and apoptosis (27). Some types of signal transduction inhibitors include Imatinib, Cetuximab, Tacrolimus, Panitumumab, and Sorafenib (28).

There are several aspects to targeted therapy, namely, the way it's synthesized or produced, the mechanism of action, the delivery mechanism into cells, and the efficacy or results of this treatment in cancer patients. Angiogenesis inhibitors block the formation of new blood vessels that feed and nourish cancer cells (18). This can be done through drugs that either reduce the production of anti-angiogenic factors, prevent them from binding to their receptors, or completely block their actions (19). Because about 60% of malignant tumors express high concentrations of VEGF, inhibiting the VEGF pathway has become a potential way to inhibit angiogenesis. Some ways to inhibit the VEGF pathway include antibodies directed against VEGF or VEGFR, soluble VEGFR/VEGFR hybrids, and tyrosine kinase inhibitors (16). The most used VEGF inhibitor on the market today is Bevacizumab or its brand name, Avastin. The article, "Bevacizumab (Avastin)", states that using Bevacizumab significantly increases overall survival in patients with metastatic breast cancer (30). Most of the production of monoclonal antibodies relies on the production of hybridomas which involves identifying plasma cells that produce antibodies to a specific antigen and fusing these cells with myeloma cells. Then, this mixture of cells is diluted and clones of these cells are grown from single parent cells on microtitre walls. The most productive and stable clones are selected for future use. The hybridomas are grown in a cell culture medium which is enriched to maximize hybridoma growth. After this, the desired antibodies are extracted. First, the sample is conditioned, or prepared for extraction. Cells, cell debris, lipids, and clotted material are removed by centrifugation, and larger particles are removed by filtration. If the concentration of the product in the sample isn't sufficient, either ultrafiltration or dialysis is performed (22). MAbs deliver molecules by themselves or molecules with drugs into or onto the cancer cell to kill it (23). Proteasome inhibitors disrupt normal cell functions so that cancer cells die. They prevent the deterioration of pro-apoptotic factors such as the p53 protein, allowing the activation of programmed cell death in neoplastic cells (26). Signal transduction inhibitors disrupt cell signals so that they change the actions of cancer cells and prevent them from proliferating (29).

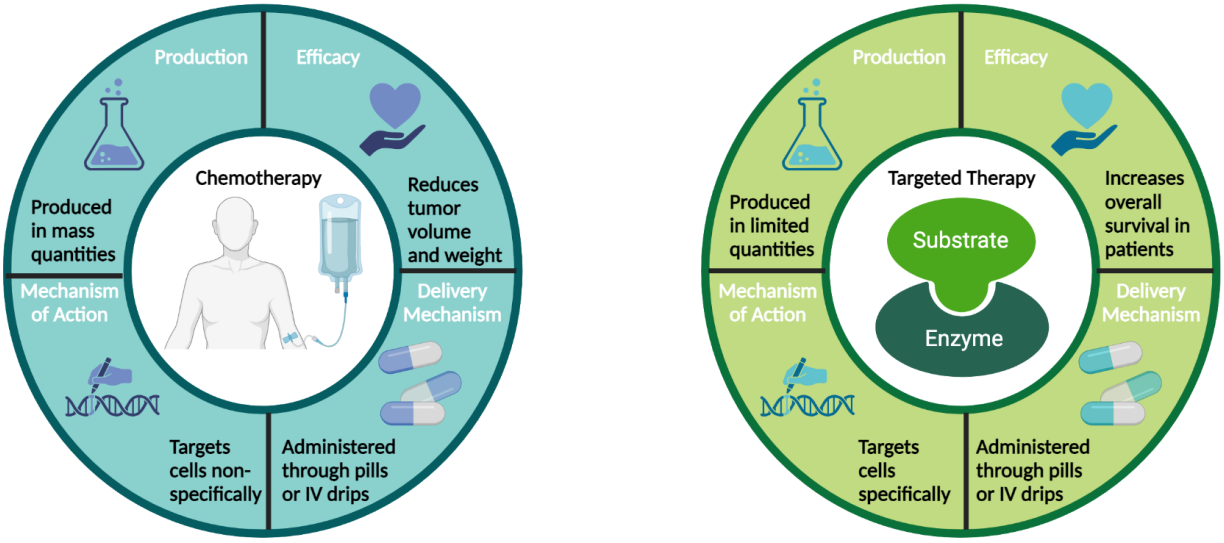

Figure 1: This figure illustrates the various aspects of chemotherapy and targeted therapy, namely the way they're synthesized, the mechanism of action, the delivery mechanism into cells, and the results of these treatments in cancer patients.

The Pros and Cons of Chemotherapy and Targeted Therapy

The socioeconomic factors that affect chemotherapy and targeted therapy are cost, availability, scope, and speed. The cost of chemotherapy depends on the type of chemotherapy, the frequency and duration of the treatment, the drug doses administered, the institution where the procedure is performed, and the patient's residence. Because of this, there's no standard cost of chemotherapy, but it usually ranges anywhere from $10,000 to $200,000. Melanoma has one of the lowest costs for treatment with an average of $5,000 for women and $5,400 for men, while brain cancer has one of the highest costs for treatment with an average of $108,000 for women and $115,000 for men. Because chemotherapy is one of the most expensive treatments in the world, health insurance covers about 10 to 15 percent of the cost, depending on whether the treatment is in the form of pills, administered through IV, or other methods. For patients who don't have health insurance, hospitals offer a 20 to 30 percent discount or higher for those who can pay in cash. There are also charitable organizations that sponsor cancer patients who don't have enough money to pay for their treatment (15). Targeted therapy also depends on whether the treatment is in the form of pills, administered through IV, or other methods. They cost a monthly average of around $5,000 to $10,000 and a yearly average of around $100,000. Orphan drugs, which are used to treat rare medical conditions, can cost $300,000 or more per year. One of the most expensive immunotherapies called CAR-T cell therapy can cost up to $500,000 a year (33).

Both chemotherapy and targeted therapy have availability problems, but because there is chemotherapy for all types of cancer, there's less of a shortage of it. By 2022, around 40 states had at least one chemotherapy drug in shortage, one of the most important ones being carboplatin. Carboplatin is used to treat several cancers, including breast, lung, ovarian, and head and neck. Not only is carboplatin an effective drug, but it's also less toxic and causes fewer side effects than other available chemotherapy drugs. This shortage led to doctors

rationing the treatment by decreasing dosage sizes by 10 percent and some patients weren't even able to get their second round of chemotherapy (35). Although chemotherapy is available for all types of cancer, this isn't the case for targeted therapy. Even out of the limited list of approved targeted therapies, there are still significant shortages of them. CAR-T cell therapy is most commonly used to treat leukemias, lymphomas, and myelomas. However, there are only 70 cancer centers in the US that can prescribe CAR-T therapy for their patients. Although many patients are in need of this therapeutic, a shortage of raw materials and supply chain restraints have made it harder to manufacture in specialized labs. Patients tend to get around 1 to 2 slots a month and others don't get any. Several patients spend months on the waiting list and around 20% die before they can even receive treatment (34).

In terms of scope of use, chemotherapy targets many people, while targeted therapy is only available for a small percentage of the population. Additionally, chemotherapy and targeted therapy are different in their approaches to treating cancer. Traditional chemotherapy is cytotoxic in nature and it targets cells non-specifically, causing severe side effects such as nausea, fatigue, infection, anemia, and most commonly, hair loss. In contrast, targeted therapy, as its name suggests, specifically targets anomalies associated with a patient's cancer. Because targeted therapy only targets cancer cells, there's a high chance they don't target hair cells, so unlike chemotherapy, patients who undergo targeted therapy may not experience hair loss as one of their symptoms. For example, Pembrolizumab, or Keytruda, is an IgG4 isotype antibody that's used to treat melanoma, lung cancer, head and neck cancer, Hodgkin lymphoma, stomach cancer, and certain forms of breast cancer. It blocks the protective mechanism of cancer cells and allows the immune system to destroy them by specifically targeting the programmed cell death protein (PD-1) receptor of lymphocytes (31). The side effects of Keytruda are similar to chemotherapy in that they include nausea, fatigue, infection, and anemia, but exclude hair loss (32).

For speed, chemotherapy treatment is much faster than targeted therapy treatment. This is because there is already chemotherapy readily available for all cancers, so doctors can simply provide the patient with the correct pill or put the patient on an IV drip as soon as they walk in. However, for targeted therapy, doctors need to first find out which genetic alterations are present in a patient's cancer. First, to sequence the cancer, a biopsy needs to be performed to isolate a section of the tumor for sample processing. Then, this sample needs to be sent to a sequencing facility, which often isn't a part of a medical center. This not only adds significant time to the sequence of treatments, but also adds an additional cost since these sequencing services are often offered through private companies. Following the sequencing of the tumor sample, the data needs to be analyzed by bioinformaticians and finally, interpreted by a doctor. This procedure not only takes several weeks but is also heavily affected by the quality of the biopsy. For example, there are many instances where solid biopsies aren't feasible depending on a patient's conditions. This would require sequencing of circular tumor DNA (ctDNA) from the patient's blood, which greatly limits the sequencing depth.

Besides comparing the cost, availability, scope, and speed, there are also several other drawbacks to both treatments. One specific drawback of chemotherapy is that it causes endothelial damage to the internal carotid artery after chemoradiotherapy of the neck for Hodgkin lymphoma (31). Two drawbacks of targeted therapy are that drugs for some targets can be difficult to develop and cancer cells can become resistant to the therapy. Cancer cells can become resistant to targeted therapy either because the target changes and the therapeutic isn't

able to interact with it or because the cancer cells can find new ways to grow that don't depend on the target (36).

	Chemotherapy	Targeted Therapy
Cost (Yearly)	10,000 - 200,000 USD	100,000 - 500,000 USD
Availability	Available for all types of cancers, so there isn't as much of a shortage of it.	Available for a limited amount of cancers, so there's a significant shortage of it; many patients die before they can even receive treatment.
Scope	Usable by all cancer patients because it targets cells non-specifically; causes more severe side effects such as nausea, fatigue, infection, anemia, and hair loss.	Usable by a small number of cancer patients because it targets cells specifically; causes fewer and less severe side effects.
Speed	Quick, because doctors can immediately provide the patient with the correct pill or put the patient on an IV drip as soon as they walk in.	Slow, because finding the specific anomaly in the patient, creating a new targeted therapy, and getting it FDA-approved is not also time-consuming, but also costly.

Table 1: This table summarizes the socioeconomic factors that affect chemotherapy and targeted therapy. Targeted therapy is significantly more expensive than chemotherapy and less available to cancer patients, unlike chemotherapy which can be used by all cancer patients. However, targeted therapy results in fewer and less severe side effects than chemotherapy because chemotherapy therapy targets both cancerous and noncancerous cells, while targeted therapy only targets cancerous cells.

Solutions

The process of creating targeted therapy is difficult because it involves a lot of time and money. Whenever there's too much of a certain protein on a cancer cell, a protein on a cancer cell that isn't on normal cells, a protein that's mutated in some way on a cancer cell, or gene changes that aren't in a normal cell, targeted therapy aims to either block or turn off chemical signals that tell the cancer cell to grow and divide, change proteins within the cancer cells so the cells die, stop making new blood vessels to feed the cancer cells, trigger the immune system to kill the cancer cells, or carry toxins to the cancer cells to kill them, respectively. In order to produce a targeted therapy, we need to know the protein on the surface of the cancer cell very well. More specifically, we need to know its properties such as size, shape, stability, abundance, and chemical composition. After this, we need to know how to make a compound that actually targets this. So, we need to make a brand-new molecule that's shaped and chemically able to bind to that protein. This involves not only biology, but chemistry too. Drug delivery is an essential part of ensuring the success of a targeted therapy. We need to make sure the compound actually gets used by our body which is much harder than it sounds. In order to verify this, we need to conduct several trials through animal testing and clinical trials which is costly and time-consuming.

Even after the targeted therapy is created and FDA-approved, matching the correct one to the patient is a long, slow process because it requires a biopsy, or sample collection, molecular investigation such as sequencing, data analysis, and matching the analysis to an available drug which can take several weeks to months. For CAR-T cell therapy specifically, the

vein-to-vein time between T cell collection and infusion takes around three weeks, but can go up to five to eight weeks if there's a delay. During this time, patients can die from lack of treatment which takes up slots and wastes viable cells (33). Many companies that produce CAR-T products such as Novartis, Bristol Myers Squibb, and Janssen, are trying to increase their capacity to manufacture CAR-T cells and shorten the vein-to-vein time for patients. Many facilities manufacture CAR-T products by hand, but they're planning to use technology to automate some steps of the process to help expedite it. Some companies have already built digital platforms for CAR-T manufacturing and are working on integrating these into other facilities. These digital systems will reduce the risk of errors, allow medical records to be shared electronically, and make the manufacturing process of targeted therapy 40% faster (34).

Conclusions and Perspectives

In this paper, we compared and contrasted chemotherapy and targeted therapy through the descriptions of their different aspects, namely cost, availability, scope, and speed. Although the aim was to deduce why targeted therapy isn't more popular and if it'll replace chemotherapy altogether in the future, there actually isn't a clear answer to this question. Not only are there strengths and weaknesses to both treatments, but this topic also doesn't simply encompass the purely biological features of cancer; it also delves into the more nuanced facets of the medical world that deal with socio-economic factors, which play a crucial role in the success of chemotherapy and targeted therapy.

Although chemotherapy isn't necessarily more effective than targeted therapy and vice versa, chemotherapy is better for patients in the short run, while targeted therapy is better for patients in the long run. This is because chemotherapy is readily available for all cancers, so doctors can simply provide patients with the correct treatment as soon as they walk in. However, there's a very limited number of targeted therapies and even so, special targeted therapies need to be created to target a specific mutation in a patient's cancer. This process can take a long time which can result in the patient dying before they can even receive treatment. On the other hand, targeted therapy causes fewer side effects than chemotherapy. This is because chemotherapy targets cells non-specifically, meaning that it targets both cancerous and noncancerous cells, while targeted therapy only targets cancerous cells. This is preferable for patients in the long run since targeted therapy leaves healthy cells untouched, thus, allowing patients to experience fewer health issues than they would if they underwent chemotherapy. Having said all this, there isn't a clear answer as to whether chemotherapy is superior to targeted therapy for cancer patients at this current stage of medicine.

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