Targeted Therapy Vs Conventional Chemotherapy: A Comparative Review

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Abstract:

This article reviews the comparison between traditional chemotherapy and targeted therapy as treatment for cancer with many important factors including mechanisms of action, overall effectiveness, toxicity and side effect profile, drug resistance, costs, and availability. Chemotherapy involves nonspecific cytotoxic agents to kill rapidly dividing cells, while targeted therapy selectively modifies cellular pathways that are critical for tumor growth. Chemotherapy is generally accessible and effective against several tumors and tumor types, but generally with significant toxicity and a degree of resistance against it. On the other hand, targeted therapy using known biomarkers let oncologists deliver precision-based care, affecting targeted areas of molecular biology that result in less systemic toxicity and overall better tolerability, although its use is often limited to high cost and need for molecular diagnostics. Combination therapy is the emergence of treating patients with chemotherapy and targeted agents simultaneously. Studies have suggested that combinations of the wide range of activity of chemotherapy with the specificity of targeted agents leads to improved treatment outcomes and reduced resistance. This review brings to light the changing roles of these therapies in our quest for personalized oncology and may allow for their use in the future to significantly improve the survival and quality of life for our patients.

INTRODUCTION

Cancer is a complex disease, characterized by uncontrolled cell proliferation, resulting from mutations in genes that drive the development of cancer, oncogenes, tumor suppressor genes, and DNA repair genes. These mutations can occur from either genetics (heredity) or environmental exposure to carcinogens (smoking, radiation, viruses, or pollution, for example). An understanding of the mutations occurring in cell proliferation will result in a more focused application of therapies. Chemotherapy uses cytotoxic agents which target cells that are in the proliferation phase of the cell cycle, meaning it can affect all rapidly dividing cells and consequently produce side effects, including nausea, hair loss, and

immunosuppression. Targeted therapy, on the other hand, inhibits or promotes molecular pathways responsible for the development of the cancer: when targeting proteins or mutations that are only present in cancer cells (i.e., unique to tumors), normal cells are spared. While there have been successes seen with cancers that have specific identifiable molecular targets, there are cancers that either do not have molecular targets, or there will be resistance to the targeted therapy. Because of the limited availability of certain chemotherapeutic agents and the increased incidences of cancer across the world, we are in need of better alternatives to chemotherapy. This review seeks to evaluate an attempt to compare conventional chemotherapy and targeted therapy in terms of mechanism of action, specificity, efficacy, adverse reactions, resistance, costs, and availability.

CANCER (NEOPLASM)

Cancer is a disorder characterized by uncontrollable growth and division of cells, and can invade adjacent tissue or metastasize to other organs, including carcinomas (epithelial tissues), sarcomas (connective or supporting tissues), leukemias (blood system), and lymphomas (lymph tissues). The TNM based system classifies staging into 0 to IV, and grading describes how abnormal and quickly proliferating the cells are. Causes of cancer include hereditary and spontaneous mutations (up to 90% of cancers), lifestyle choices (smoking, obesity, certain unhealthy diets), exposure to environmental carcinogens (e.g., radiation, pollution), infections (e.g., HPV and hepatitis), dysfunctional hormones (e.g., estrogen), and weakened immune systems.

PHARMACOTHERAPY

Pharmacotherapy in cancer employs drugs to kill cancer cells, slow the growth of tumors, and/or enhance immunity.

- **Chemotherapy**

  Chemotherapy works through cytotoxic agents that kill cancer cells and healthy, fast-dividing cells; it can also provide adverse effects like nausea, diarrhea, hair loss, and immune suppression. Chemotherapy works in a variety of ways: damaging DNA strands, blocking cell division, altering hormones in the body and more.

- **Targeted Therapy**

Targeted therapy is different than chemotherapy, because it affects particular processes within cancer cells, not just the indiscriminate killing of cancer cells i.e. targeted therapy

- **Immunotherapy**

  Immunotherapy involves therapeutics that activate the immune system using check point inhibitors and CAR-T cells, and are effective in a handful of cancers, and can have immune related side effects.

- **Hormonal Therapy**

  Hormonal therapy includes agents like tamoxifen and leuprolide and are extremely effective in all hormone-sensitive cancers by blocking hormones.

- **Supportive Therapy**

  Supportive therapy is a treatment category for patients to consider and validate with decision making. There are supportive therapies for pain control through opioids and non-steroid anti-inflammatory agents (NSAIDs), anti-emetics like ondansetron and metoclopramide, and bone protectors like bisphosphonates.

Achieving Treatment Goals

Conventional chemotherapy seeks to either destroy or shrink a tumor by targeting rapidly dividing cells, but it also primarily spares normal cells. It works by interrupting and damaging the processes of DNA replication, mitosis, RNA transcription process, and protein synthesis. Successful aspects of conventional chemotherapy include its broad spectrum of activity, versatility from a variety of doses, potential quick shrinkage of tumor, cytoreductive effect, effectiveness against metastasis, overall survival improvement, availability, curative potential, ability to cross the blood-brain barrier, and cost. Limitations of conventional chemotherapy are that it is not selective, cumulative toxicity over time, and developing myelosuppression or other resistance.

Targeted therapy it works by inhibiting the cancer growth signals, blood supply, DNA repair or modifying the cancer cells so they are susceptible to being targeted by the immune system.

The advantages of targeted therapy is the accuracy and the potential for personalized treatment, less injury to normal tissues, less side effects, efficacy in genetically defined cancers, oral/injection, potentially long-term management of cancer over time, potential for combinations with conventional chemotherapy, and promotes genetic testing in the clinic. Limitations of targeted therapy include dependence on the mutation, resistance, and cost compared to chemotherapy with less access, because they are limited to very few exempted cost sharing accounts.

Mechanism of Action: Chemotherapy vs. Targeted Therapy

Chemotherapy

- Works by non-specifically targeting all rapidly dividing cells with the properties of damaging that population of cells, hull or healthy, and targets the cell cycle at different points.
- Examples of mechanisms of chemotherapeutic agents of action are DNA damage (alkylators), inhibition of nucleotide synthesis (antimetabolites), and inhibition of mitosis (mitotic inhibitors).
- The non-specificity also causes systemic toxicity (e.g., rapid division normal cells that get damaged; gastrointestinal tract, hair follicles, bone marrow).
- Time to effect is also dose-dependent for chemotherapy; however, more dosing can assist in killing tumor cells but can also worsen side effects.
- Chemotherapy agents may act (on target of cells of those properties) at a specific cell cycle phase (S-phase), but they act on cells at any point on those cells.
- Immunosuppression is a commonly occurring side-effect due to myelosuppression, so patients are at increasing risk of infection.

Targeted Therapy

- Targeted therapy works by specifically targeting the molecular drivers of cancer growth, such as proteins, enzymes, or genetic mutations found in tumor cells.
- Examples include tyrosine kinase inhibitors, which block the signaling pathways, and monoclonal antibodies, which bind specific receptors or enhance immune recognition of abnormal cells.
- Most targeted therapies require molecular diagnostics prior to initiation, as the tests help find actionable mutations (e.g., HER2, EGFR, BCR-ABL) for patient cases.

- Many of the next generation targeted agents were developed to treat patients who had previously developed resistance to prior therapies, but with increased molecular specificity.
- Many targeted agents are administered orally, which makes them more convenient and improved adherence versus intravenous chemotherapy.
- While these therapies are more selective, they are not universally applicable, as they only apply to tumors that have the appropriate genetic alterations.
- Usually less systemic effects are associated with targeted therapies; however, unique toxicities still occur such as dermatologic toxicities, hypertension, and endocrine toxicities.

Drug Resistance in Cancer Therapy

Chemotherapy Resistance

Primary Resistance: Tumor is inherently unresponsive to drugs

Secondary Resistance: Acquired during treatment

- Efflux pumps (e.g. P-glycoprotein)
- Increased DNA repair systems
- Mutation-induced resistance
- Tumor dormancy

Targeted Therapy Resistance

Primary Resistance: Lack of targetable mutations

Secondary Resistance:

- Secondary mutations preventing drug binding
- Alternative signal activation
- Loss of target expression
- Tumor heterogeneity
- Epigenetic changes

Efficacy and Treatment Response

Conventional Chemotherapy

i. Broad Reach: used for a variety of tumors that do not have specific genetic markers.
ii. Rapid Initial Response: fast tumor shrinkage in some tumors, like breast cancer.
iii. Non-specific Mechanism of Action: affects any and all dividing cells, including healthy tissues.
iv. Resistance Mechanisms: cancers evolve through drug efflux (active process of removing the drug) or enhanced DNA repair.
v. Combination Approach: often employed in combination with other treatment phases due to resistance mechanisms and toxicity.

Targeted Therapy

i. Precision based effectiveness: works well against molecular targets, such as EGFR, HER2, BCR-ABL
ii. Predictable response: performance is generally more predictable for certain targets (e.g. gefitinib for EGFR mutations).
iii. Resistance possible: mutations or pathways allow cancers to evade targeted treatments; new agents are developed as resistance mechanisms exemplify.
iv. Biomarker dependent: eligible patients must have molecular tests run to determine eligibility.

Side Effects

Chemotherapy: Affects all actively dividing cells, including normal tissue, and can cause immediate or delayed systemic side effects.

Common Side Effects

- **Hematologic:**
    - Anemia
    - Neutropenia
- **Gastrointestinal:**
    - Nausea and vomiting
    - Diarrhea
- **Other:**

- Alopecia
- Fatigue
- Infertility
- Secondary malignancies

Management: supportive care (growth factors, antiemetics, transfusions, antibiotics)

Targeted Therapy: Have less impact on normal cells (and more impact on specific targets), but have unique side effects too.
Common Side Effects

- **Dermatologic:**
  - Rash
  - Dry skin
- **Gastrointestinal:**
  - Diarrhea
  - Stomatitis
- **Endocrine:**
  - Hypothyroidism
- **Cardiovascular:**
  - Hypertension
  - Cardiotoxicity

Management: dose reduction, supportive medications, and monitoring of organ systems.

Cost & Accessibility

Chemotherapy

- Lower cost due to generic formulations

- Widely accessible in primary and secondary care sites
- Covered under many National health schemes

Targeted Therapy

- High cost due to research, patent, and complexity
- Lacking accessibility in low resource context
- Requires molecular diagnostic infrastructure
- Is not universally covered by health care coverage.

Barriers:

- High diagnostic and monitoring costs
- Oncology centers only available in specialized settings
- Access inequities to health care providers/resources

Benefits of Targeted and Chemotherapy Combination Therapy

1. **Synergistic Action**
   The combination of both agents will amplify the overall effect → Tumor shrinkage and response rate may improve significantly.
2. **Broad-Spectrum Approach**
   Targets different cell types in a tumor → Reduces risk of treatment failure based on cell heterogeneity.
3. **Bridging Gaps in Monotherapy**
   Can be useful when one agent will not sufficiently control the disease → Will lead to better disease control.

4. **Maintenance Strategy**
   The chemotherapy agent will decrease the tumor volume but the targeted agent will continue to maintain control → Longer duration of remission and overall improved survival.
5. **Dose Optimisation and Reduced Toxicities**

Target therapy allows the chemotherapy agent to be delivered at lower doses → Shrinkage of the tumor is maximized with less toxicity. Better tolerability to the treatment.

6. **Reversing Resistance Mechanisms**
   By using both agents, the development of resistance is limited → Preventing the development of drug resistance.
7. **Improved Survival Outcomes**
   Many studies show improved PFS and OS in these groups → Improvements in overall outcomes out to 2 and 5 years.
   Examples:
   i. **Breast Cancer:** Trastuzumab + Docetaxel (HER2-positive)
   ii. **Colorectal Cancer:** Bevacizumab + FOLFOX
   iii. **Non-Small Cell Lung Cancer (NSCLC):** Osimertinib + platinum-based chemotherapy
   iv. **Ovarian Cancer:** Bevacizumab + Carboplatin/Paclitaxel
   v. Neoadjuvant and Adjuvant Treatment
   Can be used both before and after surgery → Better surgery results or recurrence possible.
8. **Cancers that are Refractory or Relapsed**
   Useful when chemotherapy fails to achieve complete response → Second-line agent when patient has resistant cancer.

Result And Discussion : Targeted Therapy Vs Conventional Chemotherapy

- Mechanism of action and specificity
  Conventional chemotherapy - cytotoxic agents, e.g., anti-metabolites, - acting nonspecifically on all rapidly-dividing cells, destroys normal and cancer cells, alike. Targeted therapy - using agents that act on specific molecular targets such as EGFR, HER2. The specificity provides a more certain action, and toxicity is lower, but biomarkers required.
- Efficacy and treatment response
  Chemotherapy - usually immediate responses for aggressive cancers; hence, examples exist as to why most patients will not long utilize therapy due to cumulative toxicity leading to resistance.

Targeted therapy - durable response for patients with known biomarker; although not responsive if the patient does not have target mutation.

- Side effects

  Chemotherapy - systemic toxicity can give subsequent myelosuppression, nausea, toxicity to other organ systems;

  Targeted therapy - generally less systemic toxicity, but pathway-specific toxicity may give skin rash, diarrhea, hypertension - and monitoring required.

- Drug resistance

  Conventional chemotherapy - resistance mechanisms commonly described ineffective efflux pumps and improved repair mechanisms, as well as target change

  Targeted therapy - resistance due to mutations (e.g. T790M), pathway switches - monitoring required through biopsy

- Cost and access

  Conventional chemotherapy - much lower cost, and generics available, and no diagnostics required

  Targeted therapy - because of development cost, patents and diagnostic required costs are higher and accessibility limited in rural population

- Monitoring and follow up

  Conventional chemotherapy - standard protocols for follow-up

  Targeted therapy - must be monitored closely with frequent testing for evidence of resistance, and required genetic profiling.

- Tumor heterogeneity

  Conventional chemotherapy - tumor heterogeneity not a factor

  Targeted therapy - less effective if tumor exhibits multiple evolving mutations.

Discussion

- Paradigm Shift From non-specific chemotherapy to biomarker-driven targeted therapy.
- The role of chemotherapy Still important for non-targetable, rapidly growing cancers. Advantages: Broad action, rapid onset. Disadvantages: High toxicity, negatively impacts quality of life.

- The role of targeted therapy Allows for personalized medicine. Advantages: Highly effective, reduced toxicity. Disadvantages: Not universally used, resistance factors - including normal cellular response to hyperproliferation, cost, need for special testing, reliability of new testing.
- Immunotherapy Activates immune system; different toxicities. Targeted immuno-oncology side effects (irAEs).
- Risk-benefit assessment Individualized treatment decisions that consider cancer type, biomarker, cost, side effect profile, and patient choice.
- Forward Directions New targets and new drugs. Better biomarker diagnostics -- better tests, or even liquid biopsy. Research resistance mechanisms. Improve cost and access internationally.

CONCLUSION

Current cancer therapy relies primarily on chemotherapy, which works by targeting cells that are rapidly dividing and is applicable to a wide variety of cancer types. While chemotherapy is widely and often successfully used for patients with cancer, there are several caveats, such as side effects which include hair loss, nausea, immunosuppression, and organ toxicity; also, over time there is decreased efficacy due to drug resistance. Targeted therapy, however, targets a specific variant or molecular abnormality that exists in a cancer cell, providing improved specificity and at times, fewer side effects. Targeted therapies are, however, expensive, can apply only to genetically characterized cancers and cannot address every tumor type. Recent advances in research have demonstrated that the combined or optimized use of chemotherapy, targeted therapy and immunotherapy can produce a more favorable result than each form of therapy can produce individually; and with higher response rate to chemotherapy, improved delay of resistance, and less toxicity, including fatigue, nausea, and other complications. Evidence has been generated in support of this integrated and multimodal system of care in HER2 positive breast cancer as well as in limited stage non-small cell lung cancer. The potential of the most effective future cancer treatment will be personalized and account for the tumor's genetics and the specific characteristics of the patient receiving the therapy, which will be therapeutic, safe, and patient-centered.

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