

Combination Therapies: Balancing Efficacy and Adverse Events

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ABSTRACT

Cancer is one of the leading causes of death worldwide and is characterized by the unregulated proliferation of mutated cells, tumor development, and, in many cases, metastasis to distant sites. Cancer treatment is often difficult because pre-existing mutations and genetic instability allow malignant cells to accumulate additional mutations, evade normal regulatory signals, and develop resistance to therapy. Common treatments, including chemotherapy, small-molecule inhibitors, monoclonal antibodies, and immunotherapies, target cancer cells through different mechanisms and may be used alone or in combination to reduce tumor size and prevent further proliferation. However, many of these treatments can cause unwanted side effects because of systemic cytotoxicity, off-target effects, or immune-related toxicity, leading to ongoing efforts to improve treatment efficacy while reducing harm to patients. Combination therapies, including antibody-drug conjugates, targeted therapies combined with chemotherapy, and targeted therapies combined with immunotherapy, aim to target multiple proteins or pathways, enhance antitumor immune responses, reduce resistance, limit immune suppression, and prevent further proliferation and metastasis. Although these approaches can improve survival outcomes and reduce tumor burden more effectively in some cancers, they may also cause more severe side effects due to overlapping toxicities. This review explores different combinations of targeted therapies and immunotherapies to evaluate their effectiveness while also assessing their potential drawbacks related to adverse effects.

Keywords: Cancer treatment, combination therapies, immunotherapies, small molecule inhibitors, antibody drug conjugates

INTRODUCTION

Cancer is a complex disease broadly characterized by uncontrolled cellular proliferation. Since 1937, it has remained the second leading cause of death, accounting for more than 10 million deaths globally in 2020 alone. (1) Approximately 90% of cancer-related deaths are attributed to metastatic disease, in which malignant cells spread from the primary tumor to distant sites in the body. (2) In addition to its substantial

mortality burden, cancer also imposes significant economic costs. The National Cancer Institute estimated that cancer-related costs in the United States reached \$208.9 billion in 2020. (3)

Under normal physiological conditions, cells tightly regulate their growth, division, and death. Cancer cells, however, acquire mutations that alter gene function and disrupt normal cell-cycle control, resulting in unregulated proliferation and harm to the organism. (4) These mutations can arise from exposure to environmental carcinogens, inherited genetic factors, or the gradual accumulation of genetic damage with age. As cancer develops, malignant cells acquire mechanisms that promote survival under adverse conditions. These include sustained proliferative signaling, resistance to growth-suppressive signals, evasion of apoptosis, and induction of angiogenesis. (5) Collectively, these adaptations enable cancer cells to obtain nutrients, bypass normal regulatory systems, and continue proliferating within the body. In advanced stages of disease, cancer cells may also metastasize to distant tissues and organs. In many cases, metastasis significantly limits the effectiveness of surgery as a curative treatment. (3)

Chemotherapy is a common cancer treatment that uses cytotoxic drugs to target rapidly dividing cells. Although these drugs are often effective against cancer cells because of their high proliferative rate, chemotherapy can also damage normal, healthy tissues that undergo frequent division, such as bone marrow, gastrointestinal epithelium, and hair follicles. (6) Many chemotherapeutic agents damage cellular DNA or interfere with the cell cycle, thereby killing rapidly proliferating cells. However, side effects can occur because of the limited specificity of cytotoxic drugs. These effects may include hair loss, fatigue, nausea, and immunosuppression, highlighting the systemic toxicity associated with conventional chemotherapy. (7)

Targeted therapies are designed to act on specific molecular features that support cancer cell survival and proliferation, rather than broadly targeting all rapidly dividing cells. These therapies are developed by identifying pathways or proteins that are altered, overexpressed, or otherwise essential in cancer cells. Such molecular abnormalities can serve as biomarkers for treatment selection and as therapeutic targets. By interfering with these targets, targeted therapies may inhibit tumor growth, induce apoptosis, or sensitize cancer cells to other treatments. (8) Major categories of targeted and immune-based therapies include small-molecule inhibitors, monoclonal antibodies, and immunotherapies. (9) Small-molecule inhibitors block intracellular signaling pathways that contribute to tumor growth and survival. These drugs are often developed to selectively bind and inhibit proteins involved in cell-cycle regulation, proliferation, or survival signaling. A common class of molecular targets is protein kinases, which regulate phosphorylation-dependent signaling cascades and may become dysregulated in cancer cells. Tyrosine kinase inhibitors block kinase activity and prevent downstream signaling pathways that promote cell-cycle progression and tumor growth. (10) For example, several targeted therapies have been developed against HER2-positive breast cancer, in which overexpression or amplification of HER2 promotes excessive growth signaling. HER2 is a receptor tyrosine kinase that signals through dimerization with other members of the HER family. Pertuzumab, although not a tyrosine kinase inhibitor, is a monoclonal antibody that binds HER2 and helps prevent receptor dimerization, thereby inhibiting downstream proliferative signaling. Pertuzumab has been used in HER2-positive breast cancer

and has also been studied in patients with metastatic disease, including those with brain metastases, demonstrating the therapeutic importance of disrupting HER2-mediated signaling in selected cancers. (11)

Monoclonal antibodies can also be used as part of targeted or immunomodulatory therapies to enhance recognition and elimination of malignant cells. This approach is important because many cancer cells evade immune detection or resist immune-mediated destruction. Some antibodies bind antigens on the cancer cell surface, allowing immune cells to identify and kill malignant cells more effectively. Others interfere with signaling pathways or modulate the tumor microenvironment, including by inhibiting angiogenesis or altering immune activity within tumors. (12) Similar to small-molecule inhibitors, monoclonal antibodies can be designed by identifying proteins expressed on malignant cells and generating antibodies with specificity for those targets. Immunotherapy is an important treatment approach because many cancers establish a tumor microenvironment that suppresses immune responses. (13) Cancer cells may evade immune surveillance through local immune suppression, production of immunosuppressive molecules, development of immune tolerance, reduction of cell-surface antigen presentation, and disruption of T-cell signaling. When malignant cells are not effectively recognized or eliminated by the immune system, they can continue dividing and contribute to an increasingly immunosuppressive tumor phenotype. Overall, targeted therapies and immunotherapies have significantly improved outcomes for many cancer patients by increasing treatment specificity and, in some contexts, reducing toxicity compared with conventional chemotherapy. (14)

Despite these advances, cancer cells often evade treatment through the accumulation of mutations and the development of therapeutic resistance. This resistance can lead to recurrence, disease progression, and more aggressive metastatic cancer following treatment. (15) For example, vemurafenib is a small-molecule inhibitor used to target mutant BRAF signaling in melanoma. Initially, BRAF inhibition can suppress downstream proliferative signaling and kill many malignant cells. However, during treatment, melanoma cells may develop resistance by activating alternative signaling pathways or acquiring additional molecular changes that bypass dependence on BRAF. As a result, even a previously effective therapy such as vemurafenib may eventually fail to control tumor growth. (16) This resistance is a common challenge in cancer treatment because genetic instability and tumor heterogeneity allow resistant subclones to survive and expand under therapeutic pressure. Resistance can lead to cancer recurrence and permit more aggressive cells to continue proliferating, potentially resulting in highly metastatic disease after treatment. Once resistance develops, previously effective therapies may lose their clinical benefit, limiting the long-term effectiveness of targeted treatment when used alone. (17)

In response to therapeutic resistance, combination therapies are increasingly used to reduce the ability of malignant cells to develop alternative strategies for survival and proliferation. Many drug combinations are being investigated to improve treatment efficacy and delay or prevent resistance. Vertical inhibition targets multiple components within a single signaling pathway, reducing the likelihood that cancer cells can bypass inhibition through downstream or upstream pathway activation. Horizontal inhibition targets multiple pathways simultaneously, limiting the ability of cancer cells to rely on alternative survival mechanisms. Both approaches may reduce resistance, improve survival, and decrease recurrence.

Combination treatment can also address the diverse cell populations present within a single tumor, thereby increasing the likelihood of a broader therapeutic response. (18) For example, neoadjuvant chemotherapy for cervical cancer has been reported to reduce the risk of death by 35% and increase survival by 14%. (19)

METHODOLOGY

In this narrative literature review, I evaluate the effectiveness of different combinations of targeted cancer therapies and assess how these combinations may reduce tumor size while also limiting the development of resistance. I also examine the increased risk of adverse effects associated with combination approaches in order to evaluate whether their therapeutic benefits outweigh their potential complications.

Literature searches were conducted between February 2026 and May 2026 through Google Scholar and PubMed. The search terms used are as listed: combination cancer therapy, antibody-drug conjugates, chemotherapy, targeted therapy, immunotherapy, increased toxicity, and adverse events. The inclusion criteria were peer reviewed, full free access texts that were written within the last 10 years. Papers that fit the inclusion criteria were selected by a brief review of the abstract and the relevance of their evidence to the goal of this review.

ANTIBODY DRUG CONJUGATES

Antibody-drug conjugates (ADCs) are anticancer therapies that combine the targeting ability of monoclonal antibodies with the cytotoxic activity of potent drug payloads demonstrated in Figure 1. In an ADC, a monoclonal antibody (labeled as orange in Figure 1) is chemically linked to a cytotoxic molecule (labeled as blue in Figure 1), allowing the treatment to selectively bind cell-surface antigens that are highly expressed on malignant cells. After binding, the ADC is internalized, and the payload is released inside the cell, where it can induce apoptosis by damaging DNA, inhibiting mitosis, or disrupting other essential cellular processes. This design allows ADCs to produce more selective cytotoxic effects than conventional chemotherapy. The cytotoxic payload is not usually designed to target proteins that are overproduced in cancer cells; rather, the antibody directs the payload to cancer cells that express the target antigen. Once released, the payload can inhibit proliferation and promote cancer cell death. Some ADC payloads can also diffuse into nearby tumor cells and kill surrounding malignant cells, a phenomenon known as the bystander killing effect. This effect may be especially useful in solid tumors, where not all cancer cells express the target antigen at the same level. Each ADC also has a specific drug-to-antibody ratio (DAR), which influences its potency, stability, toxicity, and therapeutic activity. In addition to delivering a cytotoxic payload, the antibody component of an ADC may also contribute immune-mediated effects, depending on the antibody and target involved. (20)

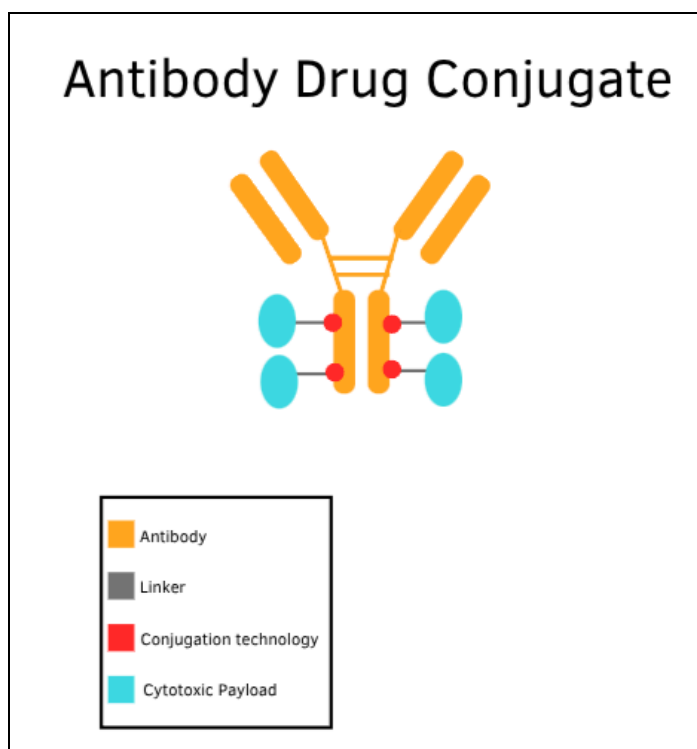


Figure 1. Structure of an antibody drug conjugate. The orange section represents the monoclonal antibody, which binds to tumor-associated antigens on cancer cells. The blue sections represent the cytotoxic payloads, which are released after internalization and induce cancer cell death. The gray sections represent the linkers, which connect the antibody to the payload and help maintain ADC stability until drug release. The red sections represent conjugation sites or conjugation technologies, which influence payload attachment and help determine the drug-to-antibody ratio. Adapted from (21).

ADCs are used in several cancers, including metastatic breast cancer. One example is trastuzumab deruxtecan, an ADC used in HER2-positive breast cancer. Aggressive HER2-positive breast cancer cells frequently overexpress the HER2 gene, resulting in high levels of HER2 receptor protein on the cell surface. Trastuzumab, the antibody component of trastuzumab deruxtecan, binds to HER2-expressing cells and helps direct the cytotoxic payload to the tumor. Although trastuzumab alone has been successful as a targeted therapy, studies have shown that combining HER2-directed targeting with cytotoxic therapy can improve treatment outcomes. (22) In trastuzumab deruxtecan, the antibody is linked to deruxtecan, a topoisomerase I inhibitor. The DAR of trastuzumab deruxtecan is approximately 8:1, meaning that each antibody carries a relatively high number of cytotoxic payload molecules. This contributes to its strong antitumor activity, while the HER2-targeting antibody helps concentrate the drug in HER2-expressing cells. The deruxtecan drug inhibits topoisomerase I, which is an essential component to DNA replication and cell division, reducing proliferation of breast cancer cells and ultimately apoptosis. The trastuzumab antibody disables proteins essential for cell division. Both of these components of the ADC target cellular

DNA. Deruxtecan inhibits topoisomerase I, an enzyme required for DNA replication and cell division. By interfering with this process, the payload causes DNA damage, reduces proliferation, and promotes apoptosis in breast cancer cells. Deruxtecan is also membrane-permeable, allowing it to diffuse into nearby tumor cells and produce a bystander killing effect. Therefore, trastuzumab deruxtecan demonstrates how ADCs can combine the specificity of antibody-based targeting with the cytotoxic effects of chemotherapy-like payloads. This approach may increase treatment effectiveness by improving drug delivery to malignant cells while reducing some of the systemic toxicity associated with conventional chemotherapy. (23)

ADCs are also used in hematologic malignancies, including leukemia. This is important because it can be difficult to selectively eliminate malignant blood cells without damaging normal blood cell populations. One example is inotuzumab ozogamicin, an ADC used in certain leukemias. The antibody component binds to CD22, a protein expressed on malignant B cells. After binding and internalization, the cytotoxic payload, ozogamicin, induces DNA strand breaks, preventing replication and promoting apoptosis in malignant cells. (24)

Brentuximab vedotin is another ADC used in Hodgkin lymphoma, systemic anaplastic large cell lymphoma, and other CD30-positive lymphoproliferative disorders. These cancers express CD30 on the cell surface, allowing the antibody component of brentuximab vedotin to bind selectively to malignant cells. After internalization, the vedotin payload is released and disrupts microtubule function, leading to cell-cycle arrest and apoptosis. Although brentuximab vedotin acts through a different cytotoxic mechanism than some other ADCs, it follows the same general therapeutic strategy: the antibody identifies cancer cells through a specific surface antigen, while the payload induces cell death after internalization. This allows chemotherapy-like cytotoxicity to be delivered more selectively to malignant cells. (25)

Patients receiving ADCs often show improved outcomes compared with those receiving only a monoclonal antibody or conventional chemotherapy. (26) This benefit is largely due to the selective delivery of cytotoxic payloads and the combined effects of antibody targeting and intracellular cell killing. However, because ADCs contain highly potent cytotoxic agents, they can still cause significant adverse effects. Toxicity may occur when the payload affects normal cells, when the target antigen is also present on healthy tissues, or when the payload is released before reaching the tumor. Therefore, although ADCs are designed to be more selective than traditional chemotherapy, they are not free from systemic toxicity. (27) Some ADCs have been associated with high rates of adverse events, including severe or life-threatening toxicity. Reported toxicities may include gastrointestinal, hematologic, respiratory, and neurologic adverse events, many of which are related to the cytotoxic payload or off-target effects. (28) For example, in patients with metastatic breast cancer, sacituzumab govitecan improved progression-free survival (PFS) to 5.6 months compared to 1.7 months with chemotherapy. Overall survival (OS) was 12.1 months with sacituzumab govitecan and only 6.7 months with chemotherapy. Both data points showed that the antibody drug conjugate was more promising for PFS and OS than the chemotherapy. (29) These results were promising due to the sample size of 468 patients, allowing for widespread use of this ADC.

The limitations of this work were that only 61 out of the 468 patients had brain metastases and data for PFS and OS was collected for less than a year. Further research is needed to evaluate the effectiveness of treatment on patients with brain metastases and the development of resistance. Throughout the experiment, clinicians also had to consider that treatment was associated with adverse effects such as leukopenia and neutropenia. (29) These findings highlight both the promise and limitations of ADCs: they can improve treatment efficacy through targeted cytotoxic delivery, but their toxicity must be carefully managed to ensure that therapeutic benefits outweigh treatment-related risks. (29)

TARGETED THERAPIES & CHEMOTHERAPY

Targeted therapies, including small-molecule inhibitors and monoclonal antibodies, can be combined with chemotherapy to enhance antitumor activity by disrupting cancer cell survival pathways while also reducing the overall number of malignant cells through cytotoxic effects. Combining these approaches allows treatment to block specific cellular pathways or functions while chemotherapy kills rapidly dividing cells. As a result, these combinations may reduce tumor size and improve survival outcomes in some patients. However, combined treatment can also increase toxicity and produce more severe adverse effects than either therapy alone. (30)

Monoclonal antibodies such as bevacizumab can be used with chemotherapy to target tumor-associated pathways that support cancer growth. Bevacizumab binds vascular endothelial growth factor A (VEGF-A), preventing it from interacting with VEGF receptors on endothelial cells. This inhibits angiogenesis, the formation of new blood vessels that supply tumors with oxygen and nutrients and may support tumor growth and metastasis. In colorectal cancer, blocking VEGF-A can reduce the vascular support available to cancer cells, limiting their ability to survive and proliferate (31) When bevacizumab is combined with cytotoxic chemotherapy, the therapies may work together by both restricting tumor blood supply and directly killing rapidly dividing cancer cells. Chemotherapy regimens such as FOLFIRI and FOLFOX have shown effectiveness in colorectal cancer when used with bevacizumab, although these combinations can also cause adverse effects. Bevacizumab-based therapy has also been studied or used in cancers that depend heavily on angiogenesis, including non-small-cell lung cancer (NSCLC) (32), metastatic breast cancer (33), glioblastoma multiforme (34), and ovarian cancer (35). These examples demonstrate how antibodies that target specific tumor-supporting mechanisms, such as angiogenesis, can complement chemotherapy and potentially reduce the burden of malignant cells in the body. (31)

Another common strategy combines chemotherapy with small-molecule inhibitors, such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, including erlotinib or gefitinib. This approach has been studied in NSCLC, a common form of lung cancer in which some tumors contain activating EGFR mutations. Both chemotherapy and EGFR tyrosine kinase inhibitors have been used individually to treat NSCLC, but more recent studies have evaluated whether combining these therapies can improve outcomes while also assessing the risk of overlapping toxicities. One study showed that combining chemotherapy with an EGFR tyrosine kinase inhibitor improved PFS, suggesting that the two approaches

may be more effective together than either approach alone in selected patients. (36) In that study, patients receiving combination therapy had a PFS of 20.5 months, compared with 15 months in patients receiving EGFR tyrosine kinase inhibitor therapy alone. The 92 patients selected for this treatment had stage III or IV EGFR activated NSCLC, with 75% having smoked in their life. However, although PFS improved, the combination did not improve OS and was associated with increased toxicity. Reported side effects included anemia, rash, neutropenia, nausea, reduced appetite, and diarrhea, with no treatment-related deaths reported. These toxicities were generally manageable and were not substantially different from those expected with chemotherapy or EGFR tyrosine kinase inhibition alone. The fact that there is no improvement in OS compared to the EGFR tyrosine kinase monotherapy shows that this combination therapy poses questions about whether the improvement is clinically meaningful enough to justify additional toxicity. The lack of OS rates may reflect several factors, such as resistance developed to the EGFR TKIs, advanced stages of the NSCLC, and previous treatments. So, further testing on other stages of NSCLC would need to be conducted to determine if the OS rates could be improved with this combination therapy. This example has similar results to other studies, demonstrating that combinations of targeted therapies, such as erlotinib or gefitinib, with chemotherapy may improve disease control in NSCLC rather than just a monotherapy, but the benefit must be weighed against toxicity and the absence of a clear OS advantage in some studies. (36)

Another important combination involves poly(ADP-ribose) polymerase (PARP) inhibitors (labeled as red in Figure 2) and chemotherapy. PARP inhibitors are effective in certain cancers because they interfere with DNA damage repair, especially in tumors with defects in homologous recombination repair pathways, such as BRCA-mutated cancers. (37) PARP enzymes normally help repair single-strand DNA breaks. When PARP activity is inhibited, as demonstrated in Figure 2, DNA damage can accumulate, eventually leading to genomic instability and apoptosis, particularly in cancer cells that already have impaired DNA repair mechanisms. (38) PARP inhibitors can be combined with chemotherapy because many chemotherapeutic agents damage DNA. Chemotherapy increases DNA damage in cancer cells, while PARP inhibitors prevent efficient repair of that damage. Together, these therapies can increase the accumulation of DNA lesions, reduce cancer cell survival, and promote apoptosis. This creates a mechanistic rationale for combining PARP inhibition with DNA-damaging chemotherapy. However, one major challenge is overlapping toxicity. Chemotherapy-related adverse effects may be intensified when

combined with PARP inhibitors, especially hematologic toxicities such as myelosuppression. (38)

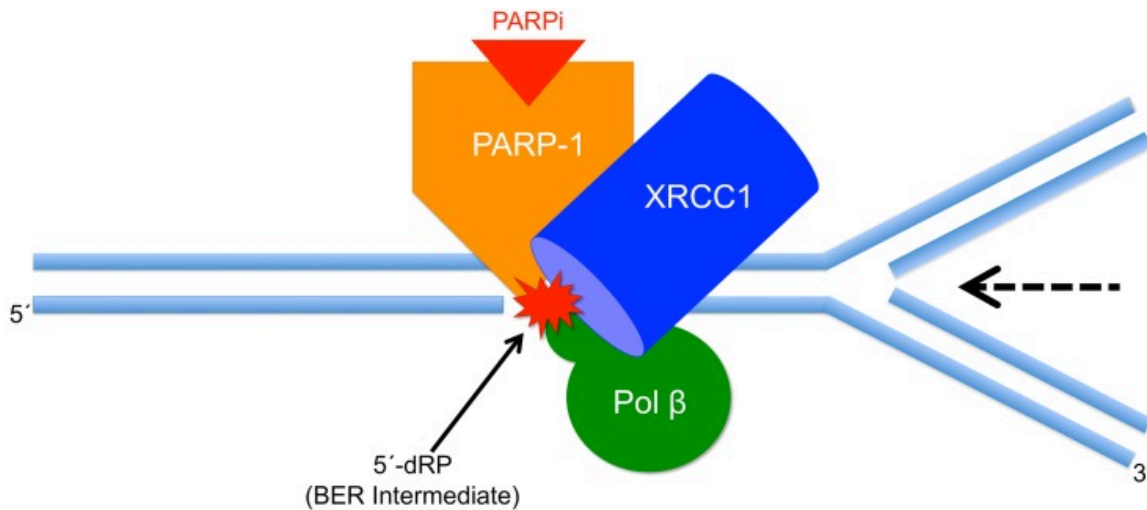


Figure 2. Structure DNA replication and the inhibition of PARP-1. This figure represents DNA replication and DNA repair in a cancer cell. PARP-1 binds to sites of DNA damage and helps recruit repair mechanisms involved in base excision repair, including BER intermediates and XRCC1. PARP inhibitors prevent normal PARP-1 activity and can trap PARP-1 on damaged DNA, thereby blocking effective DNA repair. The resulting accumulation of DNA damage can impair replication and promote cancer cell death. (38)

Overall, combinations of targeted therapies and chemotherapy can increase cytotoxicity, improve tumor control, and delay disease progression in some cancers. However, these potential benefits must be weighed against the risk of increased toxicity. Although each therapy may be effective on its own, combining them can sometimes produce overlapping adverse effects or limited improvement in OS. Therefore, evaluating both treatment efficacy and side-effect severity is essential when determining whether targeted therapy and chemotherapy combinations provide meaningful clinical benefit.

TARGETED THERAPIES & IMMUNOTHERAPIES

Targeted therapies and immunotherapies are effective treatment strategies for many cancers, but they act through different mechanisms and have distinct advantages and limitations. Targeted therapies, including small-molecule inhibitors, often produce rapid clinical responses by blocking oncogenic pathways or proteins that are abnormally activated in cancer cells. This can reduce tumor growth and improve disease control. However, cancer cells may develop resistance to targeted therapies through secondary mutations, activation of alternative signaling pathways, or changes in protein expression. As a result, the treatment may become less effective over time, allowing tumor progression to resume. In contrast, immunotherapies enhance the immune system's ability to identify and eliminate cancer cells. For example, immune checkpoint inhibitors can restore T-cell activity against tumors, while chimeric antigen

receptor T-cell therapies, or CAR-T cell therapies, engineer T cells to recognize specific tumor-associated antigens. (39) These approaches may produce durable responses because they promote antitumor immune surveillance. However, immunotherapies may take longer than small-molecule inhibitors to produce a measurable reduction in tumor size (40) In addition, not all cancers respond effectively, particularly if the tumor grows or metastasizes rapidly before a strong immune response develops. (41) Therefore, targeted therapies and immunotherapies each have important benefits and limitations: targeted therapies may act quickly but are often limited by resistance, whereas immunotherapies may produce longer-lasting immune control but can have a slower onset of action. Combining targeted therapy with immunotherapy may help overcome some of these limitations. Small-molecule inhibitors can alter the tumor microenvironment by reducing oncogenic signaling, decreasing immunosuppressive signals, inhibiting angiogenesis, or increasing the expression or presentation of tumor antigens. These changes may make tumor cells more visible and vulnerable to immune attack. If immunotherapy is administered with or after targeted therapy, the immune system may be better able to recognize and destroy malignant cells. In addition, targeted therapy may initially reduce tumor burden, giving immunotherapy more time to generate a sustained antitumor response. When small-molecule inhibitors block specific pathways, cancer cells may rely on alternative pathways or express additional proteins that can potentially be recognized as tumor antigens. (42) This may help an activated immune system identify and eliminate cancer cells more effectively. As a result, combination therapy may reduce the opportunity for cancer cells to develop resistance to targeted treatment alone and may also limit tumor growth while immunotherapy establishes a durable immune response. Therefore, combining these approaches has the potential to reduce immune evasion, delay resistance, and limit metastasis in selected cancers. (43)

Metastatic melanoma is an aggressive cancer with poor prognosis, particularly after spreading to distant organs. One study reported that the five-year survival rate after diagnosis of metastatic melanoma was only 17%. (44) Melanoma is difficult to treat because melanoma cells can metastasize rapidly and develop resistance to several therapies. Many melanomas contain activating mutations in the BRAF gene, which lead to overactivation of the MAPK signaling pathway. This pathway promotes cell proliferation, survival, and resistance to apoptosis. In addition, melanoma cells can evade the immune system by reducing antigen presentation or creating an immunosuppressive tumor microenvironment. (45) Targeted therapies such as BRAF and MEK inhibitors can initially be highly effective in patients with BRAF-mutant melanoma. For example, vemurafenib inhibits mutant BRAF and can reduce MAPK signaling, which can improve OS. Even with the improvement in OS, many tumors eventually develop resistance through reactivation of the MAPK pathway or activation of alternative signaling pathways, causing these treatments to lose effectiveness. This is demonstrated in patients receiving BRAF inhibition therapy, for whom acquired resistance commonly develops and the median PFS is 5 to 7 months. (45) Immunotherapies, particularly immune checkpoint inhibitors, can produce durable responses in some patients with metastatic melanoma, but not all patients respond, and rapidly progressive disease may advance before an effective immune response is established. When used in combination, targeted therapies may increase tumor antigen expression, reduce immunosuppressive signaling, and modify the tumor microenvironment in ways that improve immune recognition. For example, vemurafenib can block oncogenic BRAF signaling and may increase the expression or presentation of melanoma-associated

antigens on tumor cells, while immunotherapy can enhance T-cell recognition and killing of those cells. (45) MEK inhibitors are also promising targets in melanoma because they act on the MAPK pathway, which is commonly activated in metastatic melanoma. Inhibiting this pathway may reduce tumor growth and alter the immunosuppressive tumor microenvironment, making cancer cells more vulnerable to immune-mediated killing. If immunotherapy is given concurrently or sequentially, immune cells may be better able to recognize and eliminate tumor cells. In this context, targeted therapies can reduce tumor burden, decrease immunosuppression, and modify the tumor microenvironment, while immunotherapies enhance immune-mediated tumor destruction. Together, these mechanisms make targeted therapy and immunotherapy combinations a promising approach for highly metastatic cancers that develop resistance quickly. (45)

In leukemia, combinations of dasatinib, a small-molecule inhibitor, and CAR-T cell therapy have been studied to improve treatment efficacy. In Philadelphia chromosome-positive acute lymphoblastic leukemia, the Philadelphia chromosome produces the BCR-ABL fusion protein, a constitutively active tyrosine kinase that promotes malignant cell survival and proliferation. Dasatinib is a kinase inhibitor that blocks BCR-ABL signaling and interferes with downstream pathways that support leukemic cell growth. CD19- and CD22-directed CAR-T cell therapies engineer T cells to recognize and destroy malignant B cells expressing these surface antigens. In one study, patients receiving chemotherapy had a complete molecular remission rate of 25%, whereas patients receiving dasatinib combined with CD19 CAR-T cell therapy had a complete molecular remission rate of 85%, and those receiving dasatinib combined with CD22 CAR-T cell therapy had a complete molecular remission rate of 76%. (46) These remission rates are promising and suggest that combining a small-molecule inhibitor with immunotherapy can improve treatment efficacy compared with chemotherapy in this setting, but are also flawed due to the small sample size. The first study receiving only chemotherapy consisted of 28 patients and the second study receiving dasatinib and CD19 CAR-T cell therapy consisted of 27 patients. Further evaluation would need to be done on a bigger sample size to determine a more accurate average complete molecular remission rate. Mechanistically, dasatinib may reduce leukemic cell survival and tumor burden, allowing engineered T cells to more effectively eliminate remaining malignant cells. This combination may therefore increase cancer cell killing, reduce disease burden, and improve complete molecular remission rates in selected patients with acute lymphoblastic leukemia. (46) This study did not specifically include any longer term follow up, limiting conclusions about the durability of the response to the treatment. Even though the patients showed complete molecular remission, the leukemia may have been able to develop resistance and cause relapse. Future studies should assess patients for at least six months to two years post treatment to see if the patients are still cancer free.

Immune checkpoint inhibitor+targeted therapy: Immune checkpoint inhibitors can also be combined with targeted therapies to restore antitumor T-cell activity and modify the tumor microenvironment. These therapies work by blocking inhibitory immune signals, such as PD-1 or PD-L1, that prevent T cells from effectively recognizing and killing cancer cells. When combined with targeted therapies, immune checkpoint inhibitors may enhance immune-mediated tumor destruction while targeted agents reduce oncogenic signaling, tumor burden, or immunosuppressive features of the tumor microenvironment. One

example is the combination of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) with PD-1 or PD-L1 immune checkpoint inhibitors. (18) Many cancers, including some non-small-cell lung cancers, rely on dysregulated EGFR signaling for continued growth and survival. This makes the EGFR pathway an important therapeutic target for small-molecule inhibitors. In one study, patients receiving nivolumab, an immune checkpoint inhibitor, in combination with erlotinib, an EGFR-TKI, had an overall response rate of 75%. However, this combination was also associated with a higher risk of interstitial pneumonitis than patients receiving EGFR - TKI monotherapy, suggesting that the sequence and timing of treatment may be important for improving efficacy while reducing toxicity. These side effects have resulted in some clinical trials being stopped early to preserve patient's health, demonstrating that there are many combination therapies still being tested and they might not all be very efficient and some may actually be more harmful than helpful.

RAS-targeted therapies are also being investigated in cancers such as NSCLC, colorectal cancer, and pancreatic cancer. (47) RAS pathway activation can contribute to immune evasion by altering cytokine production, antigen presentation, and immune checkpoint signaling within the tumor microenvironment. When RAS inhibitors are used, cancer cells may become less able to maintain an immunosuppressive environment. In combination with PD-1 or PD-L1 immune checkpoint inhibitors, this may allow activated T cells to more effectively recognize and destroy tumor cells, potentially reducing tumor size and limiting immune evasion. (18)

Overall, the goal of combining targeted therapies with immunotherapies is to weaken cancer cells and alter the surrounding tumor microenvironment so that immune cells can more effectively eliminate malignant cells. Small-molecule inhibitors can block oncogenic pathways, reduce tumor burden, and, in some cases, increase tumor antigen presentation or shift cancer cells toward alternative pathways that may make them more recognizable to the immune system. Immunotherapies then enhance immune surveillance and support sustained antitumor immune activity. Together, these mechanisms may improve tumor control and reduce resistance in selected cancers. However, this approach also has important limitations. Immunotherapies can overstimulate immune activity and cause immune-related adverse events, in which the immune system damages normal tissues. Severe immune-associated toxicities may include immune effector cell-associated neurotoxicity syndrome and B-cell aplasia, although these are more commonly associated with cellular immunotherapies such as CAR-T cell therapy than with immune checkpoint inhibitors. (48) The severe adverse events listed above due to cellular immunotherapies are very common, with some of these adverse events affecting 60% of patients recorded. But, the sample sizes listed were often in between 30-100 patients, so further studies should be conducted with larger sample sizes to have more accurate predictions about how common these adverse events are. Also, some of the adverse events could be impacted by the presence of COVID-19, with clinicians reporting that some patients during these trials had COVID-19. (48) Other overlapping toxicities reported with targeted therapy and immunotherapy combinations include thyroid dysfunction, hepatitis, pneumonitis, cardiovascular toxicity, and oral toxicities. (49) These results are fairly accurate because the targeted therapy and immunotherapy combinations were tested on a sample size of 3713 patients across various types of cancers such as melanoma and breast cancer. Although, the clinicians in this study mention

toxicities could be due to genetic factors, which must be explored more to determine if certain adverse events only happen to a specific demographic of people. (49)

CLINICAL DECISION MAKING

Although the results of combination therapies are very promising, the therapies are not suitable for every patient. Their effectiveness often depends on the molecular characteristics of the tumour, particularly when a regimen includes a targeted treatment. For example, the anti-HER2 antibody drug conjugates were only used for patients that had advanced metastatic breast cancer and had previous treatments that resulted in resistance. These patients also needed HER2 overexpression for the treatment to be effective, which is only present in 15-20% of breast cancers. (11) The strict selection of patients for ADC's demonstrates the importance of biomarkers expressed by the cancer cells because treatment is only effective if it can find the specific biomarkers on the cancer cells. What works for one variation of a cancer may not work for the other variation, which is why biomarker testing is important to figuring out who should receive the specific therapies.

Clinicians must also consider if the treatment benefits are worth the additional toxicity and adverse events. Treatments must be balanced between benefits and side effects based on the patient's goals. For example, patients with poor performance status, impaired organ function, or coexisting comorbidities may be less able to tolerate an intensive combination regimen, even if their tumour is likely to respond. Although clinicians can reduce the severity of adverse events by providing lower doses of treatment or timing the treatment differently, the side effects may become too severe and start affecting the patient's quality of life. This forces clinicians to make difficult decisions for each individual patient and doesn't allow room for generalization of cancers or variations of specific cancers.

Not only do clinicians need to decide if their patients are strong enough to tolerate side effects, but patients must consider whether the possibility of longer PFS justifies the risk of treatment-related effects on their quality of life. Further, improved PFS does not always necessarily translate into a longer OS. These treatments can be very expensive due to the personalization of treatment, so patients also have to consider the physical and financial cost of treatment. (52) Just because patients prove to be good candidates for a specific treatment, does not always mean they will receive the treatment due to their personal decisions.

The specific patients selected for combination treatments reflects how combination therapies are very personalized. Clinicians need to decide who will benefit from the treatment most by assessing if the increased PFS is worth the risk of adverse events. Combination therapies can result in higher overall toxicity for the patient, so the improvements patients experience from treatment need to be weighed with the potentially detrimental side effects that they have to endure.

CONCLUSION

Cancer treatment has changed significantly over the past several decades, shifting from a primary reliance on broadly cytotoxic chemotherapy toward more selective approaches, including targeted therapies,

immunotherapies, and antibody-drug conjugates. Chemotherapy remains an important treatment because it can effectively kill rapidly dividing cells, but its lack of specificity can damage healthy tissues and produce substantial side effects. Targeted therapies were developed to address some of these limitations by acting on specific proteins, receptors, or signaling pathways that cancer cells depend on for growth and survival. Immunotherapies further expand treatment options by enhancing the immune system's ability to recognize and destroy malignant cells. Together, these advances have improved outcomes for many patients and have made cancer treatment more personalized and biologically precise.

However, no single treatment approach is universally effective. Cancer cells are genetically unstable and heterogeneous, allowing them to develop resistance to multiple types of therapies. Resistance to targeted therapies can occur through secondary mutations and activation of alternative pathways in cancer cells. Cancer cells can evade immunotherapies by establishing an immunosuppressive tumor microenvironment, altering antigen expression or escaping immune recognition.. Meanwhile, resistance to chemotherapy can develop through several mechanisms, including DNA repair and drug efflux. These methods of resistance across various treatment types can allow tumor progression or recurrence even after an initially successful response. Combination therapies are therefore an important strategy because they can target cancer cells through multiple mechanisms at the same time, thus delaying or reducing the likelihood of treatment resistance and recurrence. For example, combinations of targeted therapies can inhibit multiple oncogenic signaling pathways, antibody-drug conjugates can deliver potent cytotoxic payloads directly to cells expressing specific tumor-associated antigens, and combining chemotherapy or immunotherapy with targeted therapies treats cancer through different approaches, leaving less room for finding ways around these treatments. By combining these approaches, treatment may reduce tumor burden more effectively, delay resistance, and improve PFS in selected cancers.

At the same time, combination therapy also introduces important challenges. Using multiple treatments together can increase overlapping toxicity, including hematologic, gastrointestinal, immune-related, neurologic, pulmonary, and cardiovascular adverse effects. In some cases, combination therapy may improve PFS without clearly improving OS, meaning that the risks and benefits must be carefully evaluated. Therefore, the success of combination therapy depends not only on whether the drugs are effective against the tumor, but also on patient selection, treatment timing, dosing, tumor biomarkers, and management of adverse effects. The goal is not simply to use more treatments, but to use biologically rational combinations that improve tumor control while maintaining an acceptable safety profile.

Future directions in cancer combination therapy should focus on improving precision. Better biomarker testing may help identify which patients are most likely to benefit from specific combinations and which patients are at greatest risk for severe toxicity. Continued research into tumor heterogeneity, resistance mechanisms, and the tumor microenvironment may also support the development of more effective treatment sequences and combinations. Artificial intelligence may contribute to this progress by helping analyze large datasets, identify potential drug targets, predict treatment response, and support earlier cancer detection. (50) However, AI should be viewed as a supporting tool rather than the central solution, and its use must be guided by clinical evidence and professional oversight. (51)

Overall, combination therapies are one of the most promising approaches for improving cancer treatment. By attacking cancer through multiple mechanisms, they have the potential to reduce tumor size, limit resistance, and improve patient outcomes. Nevertheless, their benefits must be balanced against the increased risk of toxicity. Continued advances in targeted therapy, immunotherapy, antibody-drug conjugates, biomarker testing, and treatment personalization will be essential for developing safer and more effective cancer therapies. The long-term goal is to achieve durable remission for more patients while reducing the physical burden of treatment.

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