Cancer Chemotherapy

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Abstract

Chemotherapy remains a cornerstone of modern oncology, serving as a systemic treatment capable of targeting both visible tumors and microscopic disease. This literature review provides a comprehensive overview of chemotherapy by examining its guiding principles, pharmacologic basis, clinical applications, effectiveness, limitations, and future directions. The goal is to highlight chemotherapy's importance in cancer care while also recognizing the challenges and innovations that shape its current and future use. Together, these insights emphasize chemotherapy's role as both a foundational and adaptive modality within multidisciplinary cancer care.

Introduction

Cancer is one of the leading causes of death worldwide, and chemotherapy remains a critical component of its treatment. Chemotherapy uses drugs to omit cancer cells or inhibit them from proliferating, making it effective against cancers that have spread beyond their original site. Unlike surgery or radiation therapy, which target specific areas, chemotherapy can work throughout the body. It is used in many ways, from attempting to cure cancer to shrinking tumors before surgery and subsequently eliminating remaining cancer cells. The effectiveness of chemotherapy lies in its ability to target rapidly replicating cells, the emblematic attribute of cancer. However, because some healthy cells also divide quickly, treatment can cause side effects ranging from fatigue and nausea to long-term complications such as nerve damage or cardiovascular issues. Advancements in supportive care have helped patients manage these effects, but drug resistance and several other challenges remain. Chemotherapy is not a single treatment rather a broad category encompassing many drugs, delivery methods, and schedules tailored to the patient's cancer type, stage, and health status. It can be administered orally, intravenously, by injection, or directly to a targeted area, and it is often combined with other therapies for better results. This literature review explores chemotherapy as a whole, synthesizing existing research to provide a comprehensive understanding of its scientific foundations and practical applications. It highlights the benefits and limitations of chemotherapy, as well as its ongoing development as a vital aspect of cancer treatment.

Discussion

Chemotherapy was first introduced in the mid-20th century. During World War I, chemical warfare agents such as mustard gas were used, causing severe atrophy of the bone marrow and lymphatic tissue. Mustard gas had a cytotoxic effect, meaning it could kill cells, and this led to the idea of using chemical agents to treat cancer since it is also characterized by cell growth. In the 1940s, Louis S. Goodman and Alfred Gilman at Yale studied the therapeutic effects of nitrogen mustard, a derivative of mustard gas in treating lymphoma, a type of cancer. They found that it was effective with lymphomas as it reduced the tumor masses significantly. This established the use of chemotherapeutic agents for the treatment of cancer. Chemotherapy revolutionized oncology by offering a systemic approach to target cancer cells throughout the body, rather than relying solely on surgery or localized radiation. Over the decades, chemotherapy has remained central to cancer care, even as new treatment options such as radiation therapy and immunotherapy have emerged. Despite its benefits, chemotherapy presents significant challenges. Its toxic effects on healthy cells often lead to adverse side effects, which can greatly impact a patient's quality of life. Additionally, resistance to chemotherapy drugs is a persistent obstacle that reduces long-term effectiveness for many cancers. Thus, these challenges signify the complex balance between the benefits and limitations of chemotherapy. Ongoing research continues to focus on improving chemotherapy's effectiveness and omitting its consequences. As cancer remains to be one of the leading global health concerns, understanding the role, progress,

and limitations of chemotherapy is essential for evaluating its place in modern medicine.

Principles of Chemotherapy

Chemotherapy is grounded in the principle of selectively targeting rapidly dividing cells. Unlike surgery or radiation, which act locally, chemotherapy exerts systemic effects that can eradicate both visible tumors and microscopic disease. Its applications include curative, adjuvant, neoadjuvant, maintenance, and palliative settings, making it essential across the cancer care continuum. Curative chemotherapy is aimed at completely eliminating cancer cells, achieving long-term remission and potential cure. It is commonly effective in cancers like Hodgkin's disease, testicular cancer, pediatric tumors, and certain leukemias (PubMed; National Cancer Institute). Adjuvant chemotherapy is given after primary treatments such as surgery to destroy residual microscopic cancer cells and reduce risk of recurrence. It is commonly applied in breast cancer and osteosarcoma cases (Chemocare; Cancer Council NSW; Mayo Clinic). Neoadjuvant chemotherapy is an antecedent of the main treatment in order to shrink tumors, facilitating less extensive surgery and better outcomes. This approach is seen in cancers like breast and rectal cancer (Cancer Council NSW; Cancer Center). Maintenance chemotherapy uses lower doses after initial successful treatment to maintain remission and delay relapse, particularly in leukemias and lymphomas (Chemocare; Cancer Council NSW). Palliative chemotherapy focuses on symptom relief and improvement in quality of life when cure is not possible. It can also prolong survival by shrinking tumors causing symptoms (Canadian Cancer Society; Cancer Council NSW). However, chemotherapy is limited by the collateral damage inflicted on normal proliferating tissues, leading to toxicities such as myelosuppression, mucositis, and alopecia. To improve efficacy and minimize resistance, most regimens employ combination chemotherapy, pairing agents with different mechanisms of action and non-overlapping toxicities. Foundational models include the Goldie–Coldman hypothesis which describes the probability of resistant clones emerging as well as the Norton–Simon model, which demonstrates the benefit of dose-dense therapy (Muratore et al., 2010). Despite such advances, resistance remains an intrinsic challenge, as cancer cells adapt through mechanisms including drug efflux, enhanced DNA repair, and evasion of apoptosis. Finally, the application of these principles is reflected in the way chemotherapy is dosed and scheduled, most often by body surface area and, in select cases, through individualized formulas such as carboplatin's renal-based Calvert formula. These pharmacological and scheduling concepts are exhaustively explored in the following section.

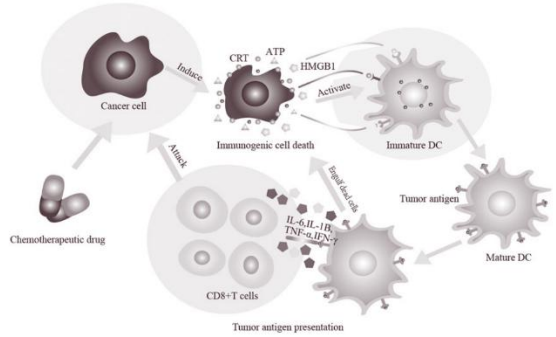

Figure 1. Chemotherapeutic drugs induce immunogenic cell death in cancer cells, leading to the release of damage-associated molecular patterns as CRT, ATP, and HMGB1. These signals activate dendritic cells which process and present tumor antigens to CD8+ T cells, thereby amplifying the adaptive immune response and enhancing the anti-tumor effects of chemotherapy. Adapted from Zhai et al., Frontiers in Pharmacology, 2023, under CC BY 4.0 license.

Pharmacology of Chemotherapy

Most chemotherapy agents are dosed according to body surface area (BSA), calculated using patient height and weight to approximate drug distribution and normalize exposure (Hoffer, 2002; Medscape, 2025; Kim, 2025). The Mosteller and Du Bois formulas are most commonly used, with the former favored for its simplicity. Despite widespread use, BSA-based dosing is controversial due to substantial interpatient variability in metabolism and elimination. Current guidelines recommend full, actual-body-weight dosing in obese adults and caution against routine BSA capping, which risks underdosing without proven safety (Griggs et al., 2012; NCCN, 2024). Carboplatin is dosed using the Calvert formula, linking exposure directly to renal clearance (Calvert et al., 1989). Several drugs rely on exposure-guided dosing or therapeutic drug monitoring (TDM). For high-dose methotrexate, serial serum levels guide

leucovorin rescue, with glucarpidase recommended in cases of delayed clearance or nephrotoxicity (Widemann & Adamson, 2006). For busulfan, AUC-targeted dosing improves engraftment and reduces relapse in HSCT (Russell et al., 2013). Pharmacokinetics further shape dosing as intravenous administration bypasses absorption barriers, distribution depends on protein binding and volume of distribution, hepatic metabolism involves enzymes such as CYP450 and UGT1A1 (notably affecting irinotecan), and renal excretion necessitates dose modification for nephrotoxic agents like cisplatin (Hoffer, 2002). Conversely, pharmacodynamics distinguishes concentration-dependent killing (such as alkylating agents and anthracyclines) from time-dependent killing (such as antimetabolites), which influences schedule design and therapeutic windows (Hoffer, 2002). Conventional 3–4 week cycles permit marrow recovery, while dose-dense regimens given every 2 weeks, validated in the CALGB 9741 trial in breast cancer, improve disease-free and overall survival (Citron et al., 2003). Metronomic therapy, involving low and frequent dosing, targets tumor angiogenesis while reducing toxicity (Browder et al., 2000). Safe dosage often depends on supportive pharmacology, such as hydration and electrolyte replacement to reduce cisplatin nephrotoxicity, mesna to prevent ifosfamide or cyclophosphamide-induced hemorrhagic cystitis, and growth factors (e.g., G-CSF) to maintain dose intensity (Bosl & Motzer, 1997; ESMO, 2020). Rescue agents like leucovorin with methotrexate are also crucial in avoiding lethal toxicities (Widemann & Adamson, 2006). Drug–drug interactions complicate therapy, for example azole antifungals strongly inhibit CYP3A4 and can cause life-threatening neurotoxicity with vincristine (Hauser et al., 2001). There is also pharmacogenomics which has become central to individualized therapy. DPYD variants necessitate 25–50 percent dose reductions for fluoropyrimidines to prevent severe or fatal toxicity (Amstutz et al., 2018). TPMT and NUDT15 polymorphisms predict thiopurine intolerance (Relling et al., 2019). UGT1A1*28 homozygotes require irinotecan dose reductions to mitigate severe neutropenia (Innocenti et al., 2004). Even formulation and route affect pharmacokinetics and clinical use. Capecitabine should be taken within 30 minutes after a meal to optimize absorption (FDA, 2023), while liposomal doxorubicin and albumin-bound paclitaxel alter distribution and clearance to improve tolerability (Gabizon et al., 2003). Collectively, chemotherapy pharmacology integrates BSA-based dosing, pharmacokinetics and pharmacodynamics principles, scheduling, supportive strategies, and pharmacogenomics to optimize efficacy, minimize toxicity, and move toward safer and more personalized treatment paradigms.

Clinical Applications of Chemotherapy

Chemotherapy is employed in multiple clinical contexts that extend beyond its basic cytotoxic mechanism, with its role tailored to therapeutic intent and disease type. Curative chemotherapy aims to eradicate all malignant cells, achieving long-term remission and potential cure. This intent has been realized in malignancies highly sensitive to cytotoxic drugs, such as Hodgkin lymphoma treated with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), testicular cancer with BEP (bleomycin, etoposide, cisplatin), and pediatric acute lymphoblastic leukemia treated with multi-agent regimens, all achieving survival rates exceeding 80% (Bosl & Motzer, 1997; National Cancer Institute, 2022). Adjuvant chemotherapy is administered after definitive local therapy, most commonly surgery, to eliminate residual microscopic disease and reduce recurrence risk. For example, anthracycline- and taxane-based regimens are standard in early-stage breast cancer following lumpectomy or mastectomy, and cisplatin-based adjuvant chemotherapy improves survival in resected osteosarcoma (Mayo Clinic, n.d.; Cancer Council NSW, n.d.). Neoadjuvant chemotherapy precedes local therapy and is used to shrink bulky tumors, thereby facilitating less extensive surgery and enabling breast-conserving approaches in breast cancer and sphincter preservation in rectal cancer (Cancer Council NSW, n.d.; Cancer Center, n.d.). Maintenance chemotherapy is administered at lower intensity after initial remission to suppress residual disease and delay relapse. It has been successfully applied in acute lymphoblastic leukemia and non-Hodgkin lymphoma, where oral agents such as 6-

mercaptopurine and methotrexate prolong remission duration (Chemocare, n.d.; Cancer Council NSW, n.d.). Finally, palliative chemotherapy is offered when cure is not feasible, with the primary goal of symptom relief, improved quality of life, and modest survival extension. For instance, gemcitabine-based regimens are commonly used in advanced pancreatic cancer to relieve tumor-related symptoms, although studies suggest that very late chemotherapy in end-stage disease may not improve quality of life and may even worsen outcomes (Canadian Cancer Society, n.d.; Cancer Council NSW, n.d.; Prigerson et al., 2015). Collectively, these applications underscore chemotherapy's suppleness across the disease spectrum.

Clinical Effectiveness of Chemotherapy

The effectiveness of chemotherapy varies widely by cancer type, reflecting differences in tumor biology, drug sensitivity, and the integration of chemotherapy into multimodality care. Certain malignancies are paradigms of chemotherapy success. In testicular cancer, cisplatin-based BEP regimens revolutionized treatment, raising cure rates from less than 10% in the pre-chemotherapy era to over 80% today (Bosl & Motzer, 1997). Similarly, multi-agent chemotherapy remains the backbone of pediatric acute lymphoblastic leukemia (ALL), where survival exceeds 85% with contemporary regimens (Hunger & Mullighan, 2015). In lymphomas, combination regimens such as ABVD for Hodgkin lymphoma and R-CHOP for diffuse large B-cell lymphoma achieve long-term disease control and cure in the majority of patients (Connors, 2005; Coiffier et al., 2002). In solid tumors, chemotherapy's impact is more variable. In early-stage breast cancer, adjuvant anthracycline- and taxane-based regimens reduce recurrence risk and improve overall survival, benefits confirmed in meta-analyses of thousands of patients (Early Breast Cancer Trialists' Collaborative Group [EBCTCG], 2012). In colorectal cancer, adjuvant fluoropyrimidine-based chemotherapy after surgical resection significantly improves disease-free and overall survival, with oxaliplatin-containing regimens (FOLFOX) establishing modern standards (Andre et al., 2004). Optimizing scheduling has also improved outcomes; for example, the CALGB 9741 trial demonstrated that dose-dense administration of doxorubicin–cyclophosphamide followed by paclitaxel significantly improved disease-free and overall survival in node-positive breast cancer (Citron et al., 2003). By contrast, in advanced pancreatic cancer, gemcitabine offers modest survival benefits, extending median survival by weeks to months, yet remains a cornerstone of palliation (Burris et al., 1997).

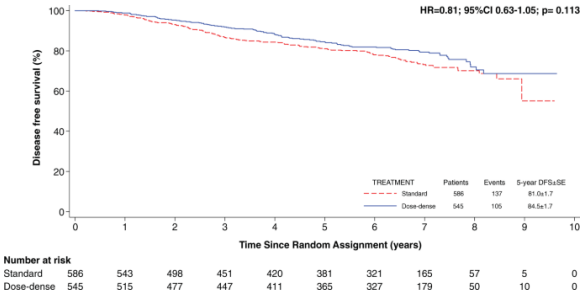

Figure 2. Kaplan–Meier plot of disease-free survival comparing standard-interval versus dose-dense adjuvant chemotherapy in hormone receptor-positive early breast cancer. Five-year DFS was 81.0% with standard therapy and 84.5% with dose-dense therapy. Adapted from Puglisi et al. (2021), npj Breast Cancer, under CC BY 4.0 license.

Chemotherapy is also essential as an adjunct to newer modalities. In HER2-positive breast cancer, the addition of trastuzumab to chemotherapy doubled survival in metastatic settings compared to chemotherapy alone (Slamon et al., 2001). In lung cancer, platinum-based chemotherapy remains the foundation of therapy, often combined with targeted agents or immunotherapy in modern protocols (Herbst et al., 2018). Even in settings where cures are elusive, chemotherapy prolongs survival, delays disease progression, and improves disease control rates. Landmark trials consistently demonstrate that when chemotherapy is integrated with surgery, radiation, or biologics, it yields superior outcomes compared to local therapy alone. Nevertheless, chemotherapy's benefit is not uniform across all tumor types; in malignancies such as metastatic pancreatic or gastric cancers, improvements remain modest, underscoring the need for continued innovation in systemic therapy. While its limitations include toxicity and resistance, chemotherapy's proven ability to extend survival and achieve cure in selected cancers establishes it as both a backbone of oncology and a partner in multimodal treatment.

Toxicities and Supportive Care

As chemotherapy exerts its therapeutic effect by targeting rapidly proliferating cells, this same mechanism characterizes its spectrum of toxicities. Acute adverse effects include myelosuppression, which predisposes to infection and anemia, chemotherapy-induced nausea and vomiting, mucositis, and alopecia (Bosl & Motzer, 1997). Chronic and organ-specific toxicities are equally significant: anthracyclines cause cumulative, dose-dependent cardiomyopathy; cisplatin induces nephrotoxicity and ototoxicity; and taxane and platinum are associated with peripheral neuropathy (Gabizon et al., 2003). Fertility impairment is also a major long-term complication, particularly in young patients receiving alkylating agents, necessitating pre-treatment counseling and preservation strategies (Canadian Cancer Society, n.d.).

Category	Side Effects
Acute	Nausea & vomiting, fatigue, hair loss, appetite/taste changes, dry mouth, constipation, mouth sores, diarrhea, infection risk (myelosuppression)
Chronic	Neuropathy (CIPN), cognitive impairment ("chemo brain"), infertility, cardiotoxicity, renal damage, secondary cancers, early menopause, weight gain

Figure 3. Table of standard, high-yield acute and chronic toxicities of chemotherapy.

Supportive care strategies have transformed the tolerability of chemotherapy. Modern antiemetic prophylaxis, guided by ASCO recommendations, combines a neurokinin-1 antagonist, a 5-hydroxytryptamine-3 receptor antagonist, and dexamethasone for highly emetogenic regimens, with olanzapine added in select cases (Griggs et al., 2012). Myeloid growth factor prophylaxis with G-CSF or peg filgrastim is indicated when the risk of febrile neutropenia exceeds 20% (NCCN, 2024). Rescue agents also mitigate lethal toxicities, as exemplified by leucovorin "rescue" after high-dose methotrexate or mesna for prevention of hemorrhagic cystitis with ifosfamide and cyclophosphamide (Widemann & Adamson, 2006). Pharmacogenetic screening is increasingly critical, with DPYD deficiency necessitating fluoropyrimidine dose reductions (Amstutz et al., 2018), TPMT and NUDT15 polymorphisms guiding thiopurine dosing (Relling et al., 2019), and UGT1A1*28 genotype informing irinotecan tolerability (Innocenti et al., 2004). Collectively, these advances illustrate how integration of supportive care, genetic testing, and toxicity monitoring has shifted chemotherapy from a purely cytotoxic to a more personalized and survivorship-conscious modality.

Combination and Multimodality Therapy

Chemotherapy rarely functions in isolation and is increasingly integrated into multimodality strategies that leverage synergy across treatment domains. In rectal cancer, fluoropyrimidines such as 5-fluorouracil act as radiosensitizers when given with concurrent radiation, improving local control and sphincter preservation (Cancer Council NSW, n.d.). Cisplatin has a similar radio sensitizing role in head and neck squamous cell carcinoma (Connors, 2005). Targeted therapies have further reshaped outcomes when added to chemotherapy, most notably trastuzumab with cytotoxic agents in HER2-positive breast cancer, which doubled survival in metastatic disease (Slamon et al., 2001). Bevacizumab combined with chemotherapy in colorectal cancer demonstrated improved progression-free survival by inhibiting angiogenesis (Herbst et al., 2018).

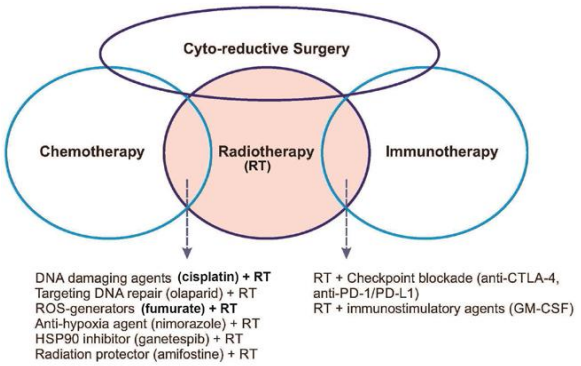

Figure 4. Schematic diagram showing the interrelationships among the four pillars of current cancer therapy, i.e., cyto-reductive surgery, chemotherapy, radiotherapy, and immunotherapy. Adapted from Chen and Kuo (2017, Figure 1).

Chemo-immunotherapy has become standard in many solid tumors, exemplified by the addition of checkpoint inhibitors such as pembrolizumab to platinum doublets in non-small cell lung cancer (Herbst et al., 2018). Antibody–drug conjugates further blur the boundary between cytotoxic chemotherapy and biologics: trastuzumab deruxtecan outperformed T-DM1 in

HER2-positive breast cancer, representing a paradigm shift in payload delivery (Puglisi et al., 2021). Locoregional intensification through hyperthermic intraperitoneal chemotherapy has also shown promise, particularly in stage III ovarian cancer following interval debulking, though adoption remains selective and evidence is evolving (van Driel et al., 2018). Together, these examples highlight that chemotherapy remains a cornerstone partner, enhancing the effectiveness of radiation, targeted therapies, immunotherapies, and novel drug conjugates.

Access, Economics, and Global Disparities

The utility of chemotherapy is tempered by uneven global access, economic constraints, and systemic challenges. The World Health Organization's Essential Medicines List includes core cytotoxics such as cisplatin, doxorubicin, vincristine, and cyclophosphamide, underscoring their global importance; however, disparities persist, with many low- and middle-income countries lacking consistent supply chains and supportive care infrastructure (Cancer Council NSW, n.d.). Even in high-income countries, recent shortages of platinum agents such as cisplatin and carboplatin disrupted standard protocols, forcing substitutions with measurable impacts on cost and outcomes (OncLive, 2023).

The financial burden of chemotherapy is also considerable, as newer formulations and combination regimens drive costs upward while generics remain variably accessible. Patients and health systems alike face "financial toxicity," compounding the physical toll of treatment. Occupational safety is another critical consideration, as healthcare workers risk hazardous exposure during compounding and administration. Regulatory frameworks such as USP <800> and the updated NIOSH hazardous drugs list mandate engineering controls, protective equipment, and handling standards to safeguard staff and patients (CDC, 2023). Addressing these systemic issues is essential to realizing the full benefit of chemotherapy globally, as inequities in drug access, affordability, and safe handling remain a major barrier to equitable cancer care.

Innovations and Future of Chemotherapy

Advances in formulation, delivery, and personalization continue to redefine chemotherapy. Liposomal doxorubicin reduces cardiotoxicity compared to conventional formulations, while albumin-bound paclitaxel enhances solubility and eliminates the need for toxic solvents (Gabizon et al., 2003). Nanoparticle-based carriers and intratumoral delivery strategies are under active investigation, aiming to enhance tumor selectivity and minimize systemic toxicity (Herbst et al., 2018). Metronomic low-dose regimens that target tumor angiogenesis offer an alternative approach with reduced toxicity and potential immunomodulatory benefits (Browder et al., 2000).

Personalization is accelerating through integration of biomarkers and pharmacogenomics. BRCA mutations confer heightened sensitivity to platinum drugs, while MGMT promoter methylation informs alkylating agent response in gliomas (Herbst et al., 2018). Universal pharmacogenomic screening, particularly for DPYD before fluoropyrimidines and UGT1A1 before irinotecan, is moving toward routine practice (Amstutz et al., 2018; Innocenti et al., 2004). Model-informed precision dosing, exemplified by AUC-guided carboplatin dosing and algorithmic strategies rooted in the Norton–Simon hypothesis, promises individualized exposure optimization (Muratore et al., 2010).

Looking ahead, antibody–drug conjugates such as trastuzumab deruxtecan and sacituzumab govitecan exemplify next-generation approaches that integrate targeted delivery with cytotoxic potency (Puglisi et al., 2021). Novel systems, including oncolytic virus-mediated chemotherapy payload delivery and implantable intratumoral chemo gels, remain experimental but highlight the innovative trajectory of the field. These innovations illustrate that chemotherapy, while among the oldest systemic anticancer modalities, continues to evolve as a precision-oriented, adaptive partner in multidisciplinary cancer care.

Conclusion

Chemotherapy remains a cornerstone of cancer therapy, providing systemic control that complements local and targeted modalities. Its principles, grounded in the selective targeting of rapidly dividing cells, have been refined through decades of pharmacologic innovation, clinical application, and supportive care strategies. While chemotherapy has delivered curative outcomes in diseases such as testicular cancer, lymphomas, and pediatric leukemias, its broader role has evolved from a standalone cytotoxic approach to an integral component of multimodality treatment. Toxicities and long-term sequelae remain major limitations, which highlights the importance of supportive interventions, dose optimization, and survivorship care. At the same time, disparities in global access and recent drug shortages emphasize the pressing need for equitable delivery of these essential therapies. And looking ahead, chemotherapy is being reshaped by innovations in drug delivery, biomarker-driven personalization, and its synergy with immunotherapy and targeted agents. Antibody–drug conjugates, liposomal formulations, and pharmacogenomic-guided dosing exemplify how the field is advancing toward greater precision and reduced toxicity. The enduring challenge is to balance efficacy with quality of life while ensuring access worldwide. Ultimately, the future of chemotherapy lies not in its continued adaptation and integration, supported by decades of clinical success and responsive to the demands of modern oncology.

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