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CANCER CHEMOTHERAPY: CONVENTIONAL APPROACHES AND RECENT ADVANCES

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ABSTRACT

Background: Cancer is a leading cause of global morbidity and mortality, characterised by uncontrolled cell proliferation, genomic instability, immune evasion, and metastasis. Chemotherapy remains a cornerstone of cancer management and is frequently combined with surgery, radiotherapy, immunotherapy, and targeted therapies. Recent advances in molecular biology and drug delivery systems have shifted treatment approaches toward precision oncology. **Objectives:** To review the historical evolution, pharmacological principles, conventional chemotherapeutic regimens, and recent advances in cancer chemotherapy. **Methods:** A narrative review of published literature, oncology guidelines, pharmacology textbooks, and recent clinical studies was conducted. Evidence regarding conventional chemotherapy, targeted therapies, toxicity profiles, and emerging therapeutic innovations was synthesised. **Results:** Cancer chemotherapy has evolved from nitrogen mustard derivatives to molecularly guided precision medicine. Conventional chemotherapy remains essential in the treatment of haematological and solid malignancies, including leukaemias, lymphomas, breast, lung, colorectal, ovarian, gastric, and other cancers. Recent advances include novel agents such as elacestrant, LiPyDau, pirtobrutinib, revumenib, and asciminib, which target resistant molecular pathways. Innovations in liposomal delivery systems, sustained-release formulations, immunochemotherapy, scalp cooling therapy, and metronomic chemotherapy have improved efficacy while reducing toxicity. **Conclusion:** The field of cancer chemotherapy is transitioning from non-specific cytotoxic therapy to personalised, targeted treatment strategies. Continued advances in molecular therapeutics and drug delivery technologies are expected to further improve survival outcomes and quality of life in cancer patients.

KEYWORDS: *Cancer chemotherapy, Conventional chemotherapy, Targeted therapy, Immunotherapy, Drug delivery, Precision medicine.*

1. INTRODUCTION

Cancer is one of the leading causes of mortality worldwide and continues to represent a major public health challenge. It is a heterogeneous and multifactorial disease characterized by uncontrolled cellular proliferation, genomic instability, angiogenesis, immune evasion, metastasis, and resistance to apoptosis.[1,2] The transformation of normal cells into malignant cells occurs through the accumulation of genetic and epigenetic alterations influenced by environmental carcinogens, chronic inflammation, altered metabolism, infectious agents, and lifestyle factors.[1,2] Recent advances in molecular biology and tumor immunology have significantly improved the understanding of cancer pathogenesis and therapeutic interventions.[3,4]

Chemotherapy refers to the treatment of systemic infections or malignancies using drugs that possess selective toxicity against infecting organisms or malignant cells while causing minimal damage to normal host tissues.[5] Cancer chemotherapy specifically involves the use of drugs to destroy cancer cells or inhibit their proliferation.[6] Chemotherapy remains one of the principal modalities of cancer treatment and may

be administered alone or in combination with surgery, radiotherapy, immunotherapy, or targeted therapy depending on the type and stage of malignancy.[1,5]

1.1 Historical Background of Cancer Chemotherapy

The concept of cancer dates back to ancient civilizations, where Hippocrates first described tumors using the term "carcinos" because of their crab-like appearance.[1] Early treatment approaches were limited to surgery, cauterization, bloodletting, and herbal remedies, with minimal therapeutic success. Significant progress in cancer therapeutics remained limited until the twentieth century.[1]

The modern era of cancer chemotherapy began during and after World War II following the observation that nitrogen mustard gas caused suppression of rapidly proliferating lymphoid and bone marrow cells.[7] Subsequent experimental and clinical studies demonstrated regression of lymphoma in patients treated with nitrogen mustard derivatives, thereby establishing chemotherapy as an effective systemic anticancer therapy.[7,8] These discoveries laid the foundation for the development of modern chemotherapeutic agents and revolutionized oncology practice.

1.2 Evolution of Cancer Chemotherapy

Cancer chemotherapy has evolved remarkably from the early discovery of cytotoxic agents to the development of highly targeted and personalized therapies used in modern oncology. The concept of chemotherapy was initially introduced by Paul Ehrlich, who proposed the idea of "magic bullets" capable of selectively targeting diseased cells.[9] A major breakthrough occurred when Sidney Farber demonstrated temporary remission in childhood acute lymphoblastic leukemia using antifolate therapy.[10]

Over subsequent decades, the discovery of alkylating agents, antimetabolites, vinca alkaloids, anthracyclines, and platinum compounds significantly improved survival outcomes in both hematological and solid malignancies.[9] The introduction of combination chemotherapy regimens further enhanced therapeutic efficacy and reduced the development of drug resistance. Advances in molecular biology during the late twentieth century led to the emergence of targeted therapies such as imatinib and monoclonal antibodies like trastuzumab, which selectively inhibit cancer-specific molecular pathways with comparatively reduced toxicity.[11,12]

More recently, immunotherapy, immune checkpoint inhibitors, antibody–drug conjugates, CAR-T cell therapy, nanotechnology-based drug delivery systems, and precision medicine guided by genomic profiling have transformed cancer management and ushered oncology into the era of personalized therapy.[13,14] Despite persistent challenges including systemic toxicity, multidrug resistance, tumor heterogeneity, and high treatment costs, the continuous evolution of chemotherapy has substantially improved cancer survival rates and quality of life worldwide.[1,9]

1.3 Basic Principles of Chemotherapy

Chemotherapeutic agents primarily act by interfering with cellular growth, replication, and survival pathways. Since cancer cells proliferate more rapidly than most normal cells, they are more susceptible to cytotoxic injury induced by anticancer drugs.[1,2] These agents may inhibit DNA replication, RNA transcription, nucleotide synthesis, mitotic spindle formation, or cellular metabolism.[5]

However, because malignant cells share several biochemical pathways with normal rapidly dividing host cells, chemotherapy often produces significant adverse effects including myelosuppression, gastrointestinal toxicity, alopecia, nephrotoxicity, pulmonary fibrosis, neurotoxicity, and cardiotoxicity.[2,15] The emergence of multidrug resistance through mechanisms such as enhanced DNA repair, altered drug metabolism, mutation of drug targets, and drug efflux pumps remains a major challenge in cancer chemotherapy.[16,17]

Modern oncology increasingly focuses on targeted therapy, immunotherapy, biomarker-guided treatment selection, and personalized medicine approaches to improve therapeutic efficacy while minimizing toxicity.[13] These advances continue to expand the scope and effectiveness of cancer chemotherapy in contemporary clinical practice.

2. CONVENTIONAL CHEMOTHERAPY IN CANCER

Cancer is a heterogeneous, multifactorial disease driven by uncontrolled genomic and molecular alterations that cause malignant proliferation. Cancer cells subvert normal signalling, evade immune surveillance, and exploit microenvironmental niches for survival.[18–23] From a therapeutic standpoint, conventional chemotherapy has remained the cornerstone of oncological practice for more than seven decades since nitrogen mustard derivatives were first shown to cause regression of lymphomatous tissue.[24–26] Subsequent decades witnessed the systematic introduction of alkylating agents, antimetabolites, vinca alkaloids, taxanes, antitumour antibiotics, and topoisomerase inhibitors, each offering distinct mechanisms and clinical applications.[27]

2.1 Classification of Conventional Chemotherapeutic Agents

Diasio (1980) described six major pharmacological classes: (i) alkylating agents, (ii) antimetabolites, (iii) antibiotics, (iv) natural products (vinca alkaloids), (v) miscellaneous agents, and (vi) hormones.[29,30] Anand et al. (2023) refined this taxonomy by including taxanes, topoisomerase inhibitors, and purine and pyrimidine antagonists as distinct subgroups.[31–34]

Alkylating agents transfer alkyl groups to guanine bases, producing DNA cross-links that prevent replication and cause irreversible cell senescence.[31,32] Antimetabolites mimic nucleotide precursors or enzyme substrates and disrupt folate metabolism, nucleotide synthesis, and DNA replication.[33,35] Vinca alkaloids inhibit microtubule polymerisation arresting cells in metaphase,[34,36] while taxanes stabilise polymerised microtubules and prevent depolymerisation, also causing mitotic arrest.[37–39] Antitumour antibiotics intercalate into DNA or inhibit topoisomerase II; camptothecin derivatives specifically inhibit topoisomerase I.[40–42]

2.2 Conventional Chemotherapy by Cancer Type

For each malignancy the principal conventional drugs, their molecular mechanisms, representative adverse effects, and current approval status are discussed -

2.2.1 Leukaemias

2.2.1.1 Acute Lymphoblastic Leukaemia (ALL)

ALL achieves remission rates exceeding 90% in paediatric patients when combination chemotherapy is used.[30] Standard induction incorporates vincristine, which inhibits tubulin polymerisation and arrests mitosis in metaphase,[34,36] daunorubicin, which intercalates with DNA and inhibits topoisomerase II,[75,76,78] and prednisone. Maintenance relies on mercaptopurine, a purine antagonist inhibiting hypoxanthine-guanine phosphoribosyltransferase, and methotrexate, an antifolate inhibiting DHFR, thereby blocking tetrahydrofolate production essential for nucleotide synthesis.[44] Cytarabine inhibits DNA polymerase beta and is incorporated into DNA.[45] Clofarabine is active in relapsed ALL, inhibiting ribonucleoside-diphosphate reductase and DNA polymerase alpha.[81] Common toxicities include myelosuppression, peripheral neuropathy (vincristine), cardiotoxicity (daunorubicin), hepatotoxicity, and mucositis.[30,75,76]

2.2.1.2 Acute Myeloid Leukaemia (AML)

The '7+3' induction (cytarabine 7 days + daunorubicin 3 days) remains the standard.[75,76] Idarubicin, an anthracycline intercalating with DNA and inhibiting topoisomerase II alpha, is approved for AML in adults. Clofarabine is approved/investigational in relapsed paediatric AML.[81] Decitabine inhibits DNA methyltransferases 1, 3A, and 3B and is approved/investigational in AML and myelodysplastic syndrome. Major adverse effects include febrile neutropenia, haemorrhagic complications, and gastrointestinal toxicity.

2.2.1.3 Chronic Lymphocytic Leukaemia (CLL)

Chlorambucil, a DNA cross-linking alkylating agent, was the standard oral first-line agent for CLL for decades.[82] Fludarabine, a purine antagonist inhibiting ribonucleoside-diphosphate reductase and DNA polymerase alpha, is central to CLL therapy.[83] The FDA-approved fludarabine + cyclophosphamide + rituximab (FCR) regimen is the benchmark for fit patients.[84] Bendamustine, producing intra- and inter-strand DNA cross-links, is approved/investigational in CLL, follicular lymphoma, mantle cell lymphoma, and Waldenström's macroglobulinaemia. Adverse effects include myelosuppression, infections, and elevated bilirubin.

2.2.1.4 Chronic Myelogenous Leukaemia (CML)

Busulfan is a bifunctional alkylating agent mainly reserved for conditioning prior to stem-cell transplantation.[85,86] Hydroxyurea inhibits ribonucleoside-diphosphate reductase and is approved for resistant CML.[87] Mercaptopurine and thioguanine retain activity in blast-crisis CML. Principal toxicities of busulfan are myelosuppression, nausea, vomiting, and loss of fertility.

2.2.2 Lymphomas

2.2.2.1 Hodgkin Lymphoma

The ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine) is the global standard for advanced Hodgkin lymphoma, demonstrating equal activity to MOPP with no cross-resistance and a superior toxicity profile.[88] Bleomycin chelates iron to generate superoxide and hydroxyl free radicals that cause DNA strand scission; it lacks myelosuppression, making it valuable in combination regimens.[79,80,89] Vinblastine arrests mitosis by binding tubulin and preventing polymerisation.[34,36] Dacarbazine is a DNA cross-linking alkylating agent approved for Hodgkin disease and melanoma.[90] Carmustine and lomustine, nitrosourea alkylating agents, are employed in relapsed/refractory Hodgkin disease.[29,91] Bleomycin toxicities include pulmonary fibrosis and skin changes; the accepted cumulative maximum dose is 400 units.[79,89]

2.2.2.2 Non-Hodgkin Lymphoma (NHL)

The CHOP platform (cyclophosphamide, doxorubicin, vincristine, prednisone) is the backbone of most B-cell NHL regimens. Cyclophosphamide is a bifunctional alkylating agent cross-linking DNA strands. Doxorubicin intercalates with DNA and inhibits topoisomerase II alpha, causing G2 arrest and apoptosis.[77,78,89] Methotrexate at high doses provides CNS prophylaxis and activity in aggressive NHL.[44] Fludarabine is active in indolent B-cell lymphomas.[83] Cytarabine is incorporated into R-DHAP and other salvage regimens.[45] Bendamustine combined with rituximab is active in follicular and mantle cell lymphoma. Key toxicities: haemorrhagic cystitis and myelosuppression (cyclophosphamide); cumulative cardiotoxicity (doxorubicin); peripheral neuropathy (vincristine); mucositis and hepatotoxicity (methotrexate).[92–94]

2.2.3 Breast Cancer

The landmark Italian CMF trial (cyclophosphamide, methotrexate, 5-FU) established adjuvant chemotherapy benefit in premenopausal breast cancer.[95] Epirubicin, a stereoisomer of doxorubicin inhibiting topoisomerase II alpha, is approved for breast cancer. Paclitaxel stabilises

polymerised microtubules by binding beta-tubulin, preventing depolymerisation and inducing mitotic arrest at G2/M.[37–39] It demonstrated efficacy in metastatic ovarian and breast carcinomas refractory to first-line therapy, and activity in head and neck disease and oesophageal adenocarcinoma.[52–54] Docetaxel is active against breast cancers resistant to first-line regimens and is approved for metastatic breast, NSCLC, gastric, and prostate cancers.[55] Capecitabine, an oral 5-FU prodrug inhibiting thymidylate synthase, is approved/investigational for metastatic breast, gastric, and colorectal cancers.[47] Gemcitabine inhibits ribonucleoside-diphosphate reductase and thymidylate synthase and is used in metastatic breast cancer.[48] Vinblastine and vinorelbine retain activity in pretreated metastatic breast disease.[34,36] Major toxicities include cumulative cardiotoxicity with anthracyclines (total doxorubicin ceiling 550–600 mg/m2),[89] peripheral neuropathy and myelosuppression (taxanes), hand-foot syndrome (capecitabine), and haemorrhagic cystitis (cyclophosphamide).[56,57,92,93]

2.2.4 Colorectal Cancer

5-Fluorouracil (5-FU), a pyrimidine antagonist inhibiting thymidylate synthase and misincorporated into RNA and DNA, is the cornerstone of colorectal chemotherapy.[46] Oxaliplatin, a third-generation platinum compound producing DNA cross-links, is the basis of FOLFOX and XELOX regimens; its defining toxicity is peripheral sensory neuropathy. Irinotecan inhibits topoisomerase I and is used in FOLFIRI; it causes cholinergic early diarrhoea and severe late secretory diarrhoea.[65,66] Raltitrexed is a thymidylate synthase inhibitor and an antagonist of folylpolyglutamate synthase, providing an alternative in fluoropyrimidine-intolerant patients.[50] Capecitabine is approved for metastatic colorectal and gastric cancers.[47]

2.2.5 Lung Cancer

2.2.5.1 Non-Small Cell Lung Cancer (NSCLC)

Platinum-based doublets are the standard first-line backbone for advanced NSCLC. Cisplatin forms intra-strand and inter-strand DNA cross-links and is active in multiple solid tumours.[96,97] Carboplatin shares the same mechanism with a more favourable toxicity profile.[98] Paclitaxel and docetaxel are approved partners for platinum in NSCLC.[37,38] Gemcitabine/platinum doublet is a standard first-line option.[48] Vinorelbine is approved for advanced NSCLC and metastatic breast cancer. Pemetrexed, a multitargeted antifolate, is approved for non-squamous NSCLC and malignant pleural mesothelioma. Principal toxicities include nephrotoxicity, ototoxicity, peripheral neuropathy, nausea, and myelosuppression.[96,99]

2.2.5.2 Small Cell Lung Cancer (SCLC)

Etoposide + platinum (EP) is the international standard first-line regimen. Etoposide, a semisynthetic derivative of podophyllotoxin, inhibits topoisomerase II by forming a ternary complex with DNA and the enzyme, inducing strand breaks and G2 arrest.[40,41,58,59] Cancer cells dividing more rapidly than normal tissues are disproportionately affected.[60,61] Topotecan, a camptothecin derivative inhibiting topoisomerase I, is approved for second-line relapsed SCLC.[62–64] Toxicities of EP include severe myelosuppression, alopecia, and cisplatin-related nephrotoxicity and ototoxicity.

2.2.6 Ovarian Cancer

Paclitaxel + carboplatin is the global standard first-line chemotherapy for epithelial ovarian cancer. Carboplatin produces DNA cross-linking/alkylation; its primary toxicities are myelosuppression, nausea, vomiting, and electrolyte disturbances.[98] Paclitaxel demonstrated confirmed activity against metastatic ovarian carcinoma refractory to first-line therapy; peripheral neuropathy and myelosuppression are dose-limiting.[52,56,57] Topotecan is established in platinum-resistant relapsed ovarian cancer.[62,63,100–102] Trabectedin, a tetrahydroisoquinoline alkaloid binding the minor groove of DNA, is approved for unresectable or metastatic soft-tissue sarcoma and is approved/investigational in ovarian cancer.[103]

2.2.7 Gastric Cancer

5-FU and capecitabine are the foundational fluoropyrimidines in perioperative and palliative gastric cancer chemotherapy. Docetaxel is incorporated into DCF and FLOT regimens. Tegafur, an oral 5-FU prodrug inhibiting thymidylate synthase, is approved as Teysuno (S-1) for advanced gastric cancer in combination with cisplatin; principal toxicities include myelosuppression, central neurotoxicity, and GI toxicity.[51,104] Mitomycin C, a bioreductive alkylating agent from Streptomyces caespitosus cross-linking DNA at adenine N6 and guanine O6 and N2, is used palliatively in gastric and other GI cancers.[70–73]

2.2.8 Pancreatic Cancer

Gemcitabine monotherapy was the standard first-line treatment for advanced pancreatic adenocarcinoma for over a decade. Gemcitabine cross-links DNA and inhibits ribonucleoside-diphosphate reductase, thymidylate synthase, and UMP-CMP kinase.[48] FOLFIRINOX and gemcitabine + nab-paclitaxel are preferred for good-performance-status patients.[46,48,65] Streptozocin, a glucosamine-nitrosourea cross-linking DNA and serving as a glucose transporter ligand, retains specific use in islet-cell neuroendocrine tumours.[105]

2.2.9 Brain Tumours

Temozolomide (TMZ) is the standard oral alkylating agent for glioblastoma multiforme and metastatic melanoma, methylating DNA at O6-guanine and inducing apoptosis in MGMT-deficient tumours.[106] Carmustine (BCNU), a nitrosourea alkylating agent, is used intravenously and as an implantable wafer (Gliadel) for glioblastoma and other brain tumours, multiple myeloma, and Hodgkin disease.[29,91] Lomustine (CCNU) is employed for metastatic brain tumours and Hodgkin disease; its principal adverse effect is

myelosuppression.[107] Etoposide is also employed in CNS tumours.[61]

2.2.10 Head and Neck Cancer

Cisplatin concurrent with radiotherapy is the backbone of curative chemoradiation for locally advanced HNSCC, and TPF (docetaxel, cisplatin, 5-FU) is the standard induction regimen.[96] Bleomycin has historical activity in squamous cell carcinomas of the head and neck, exploiting its lack of myelotoxicity.[79,80,89] Methotrexate provides palliative activity in recurrent/metastatic HNSCC.[44,108] Carboplatin replaces cisplatin in renally compromised patients.[98] Porfiromycin, an N-methyl derivative of mitomycin C, has been directly compared with mitomycin C in a randomised HNSCC chemoradiotherapy trial.[74]

2.2.11 Cervical Cancer

Cisplatin concurrent with radiotherapy is standard of care for locally advanced cervical cancer. Topotecan combined with cisplatin or paclitaxel is approved/investigational for recurrent or metastatic disease.[63,64,100] Ifosfamide causes DNA alkylation; its distinctive toxicity is haemorrhagic cystitis, mitigated by mesna.[93,109] Mitomycin C is included in selected concurrent chemoradiation protocols.[70,71] Carboplatin-based regimens are alternatives for cisplatin-ineligible patients.[98]

2.2.12 Bladder Cancer

Cisplatin-based combinations (GC: gemcitabine + cisplatin; MVAC: methotrexate, vinblastine, doxorubicin, cisplatin) are standard perioperative and palliative therapy.[48,96,99] Thiotepa is administered intravesically for superficial bladder cancer and systemically in ovarian, breast, and thyroid cancers.[110] GC provides equivalent overall survival to MVAC with a more favourable toxicity profile.[48] Carboplatin-based regimens are used for cisplatin-ineligible patients.[98] Methotrexate contributes to MVAC through DHFR inhibition.[44]

2.2.13 Testicular Cancer (Non-Seminoma)

The BEP regimen (bleomycin, etoposide, cisplatin) achieves complete remission rates exceeding 70% in disseminated non-seminomatous germ cell tumours.[111] Etoposide replaced vinblastine in earlier regimens, improving tolerability without sacrificing efficacy.[40,61,111] Ifosfamide is central to VIP salvage regimens. Actinomycin D inhibits RNA elongation by intercalating between G-C base pairs and binding the DNA minor groove, and is active in testicular tumours and gestational trophoblastic neoplasms.[67–69] Bleomycin pulmonary fibrosis risk requires cumulative dose monitoring (maximum 400 units).[89]

2.2.14 Prostate Cancer

Docetaxel + prednisone is established first-line chemotherapy for castration-resistant prostate cancer (CRPC). Mitoxantrone, an anthracenedione intercalating with DNA and inhibiting topoisomerase II alpha, provides palliative benefit in hormone-refractory prostate cancer.[112] Ixabepilone, an epothilone B analogue inhibiting tubulin beta-3 chain, is approved/investigational for prostate cancer. Taxane toxicities include peripheral neuropathy, myelosuppression, fluid retention, and nail changes.

2.2.15 Melanoma

Dacarbazine (DTIC) was the reference single-agent for metastatic melanoma for decades.[29,90] Temozolomide, with superior CNS penetration, is approved/investigational in metastatic melanoma.[106] Carboplatin + paclitaxel combinations provide activity in chemotherapy-naive metastatic melanoma.[37,98] Hydroxyurea inhibits ribonucleoside-diphosphate reductase and is approved for melanoma.[87] Melphalan, a bifunctional nitrogen mustard analogue, is employed in isolated limb perfusion (ILP) for locally advanced or in-transit melanoma.[113]

2.2.16 Neuroblastoma

Cyclophosphamide is a cornerstone of induction regimens including CAV (cyclophosphamide, doxorubicin, vincristine). Etoposide + carboplatin provides high response rates in high-risk disease.[40,61] Ifosfamide and vincristine are employed in various protocols. High-dose chemotherapy (busulfan + melphalan or carboplatin + etoposide) followed by autologous stem-cell rescue is standard consolidation for high-risk neuroblastoma.[85,113] Intensive regimen toxicities include severe myelosuppression, mucositis, haemorrhagic cystitis, and peripheral neuropathy.[92,93]

2.2.17 Wilms Tumour (Nephroblastoma)

Actinomycin D combined with vincristine and surgery achieves cure rates of 30–40% in advanced disease. Doxorubicin is added for higher-stage disease. Actinomycin D intercalates between G-C base pairs and prevents RNA elongation by blocking the transcriptional complex.[67–69] Ifosfamide, etoposide, and carboplatin are employed in relapsed disease.

2.2.18 Gestational Trophoblastic Neoplasms

Gestational trophoblastic neoplasms are among the most chemosensitive malignancies, with cure rates approaching 70% using methotrexate-based regimens. Methotrexate is the preferred single agent for low-risk disease; EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) is standard for high-risk disease.[44,67] Actinomycin D is approved for trophoblastic neoplasms.[69]

2.3 Summary Table: Conventional Chemotherapy by Cancer Type

Table 1: Conventional chemotherapy by cancer type.

Cancer Type	Key Drugs	Primary Mechanism	Status	Key References (new #)
ALL	Vincristine, Daunorubicin, Methotrexate, Mercaptopurine, Cytarabine	Microtubule inhibition; DNA intercalation; DHFR inhibition; purine antagonism	Approved/Inv.	[26]
AML	Cytarabine, Daunorubicin, Idarubicin, Clofarabine, Decitabine	DNA polymerase inhibition; DNA intercalation; ribonucleotide reductase inhibition	Approved/Inv.	[45,75,76,81]
CLL	Chlorambucil, Fludarabine, Bendamustine, Cyclophosphamide	DNA cross-linking; ribonucleotide reductase inhibition	Approved/Inv.	[82,83,84]
CML	Busulfan, Hydroxyurea, Mercaptopurine	DNA alkylation; ribonucleotide reductase inhibition	Approved	[85,86,87]
Hodgkin Lymphoma	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine (ABVD)	DNA intercalation/topo-II; DNA strand scission; microtubule inhibition; DNA alkylation	Approved	[26]
Non-Hodgkin Lymphoma	Cyclophosphamide, Doxorubicin, Vincristine, Methotrexate, Fludarabine	DNA cross-linking; topo-II inhibition; DHFR inhibition; microtubule inhibition	Approved/Inv.	[26]
Breast Cancer	Cyclophosphamide, Doxorubicin, Epirubicin, Paclitaxel, Docetaxel, Capecitabine, Gemcitabine	DNA alkylation; topo-II inhibition; microtubule stabilisation; thymidylate synthase inhibition	Approved/Inv.	[28]
Colorectal	5-FU, Oxaliplatin, Irinotecan, Capecitabine, Raltitrexed	Thymidylate synthase inhibition; DNA cross-linking; topo-I inhibition	Approved/Inv.	[46,47,50,65,66]
NSCLC	Cisplatin/Carboplatin, Paclitaxel, Docetaxel, Gemcitabine, Vinorelbine, Pemetrexed	DNA cross-linking; microtubule stabilisation/inhibition; multitarget antifolate	Approved/Inv.	[28]
SCLC	Etoposide + Cisplatin/Carboplatin, Topotecan	Topo-II inhibition; DNA strand breaks; topo-I inhibition	Approved/Inv.	[27,31–33]
Ovarian	Paclitaxel, Carboplatin, Topotecan, Gemcitabine, Trabectedin	Microtubule stabilisation; DNA cross-linking; topo-I inhibition; minor groove binding	Approved/Inv.	[31,35]
Gastric	5-FU/Capecitabine, Oxaliplatin, Docetaxel, Tegafur, Mitomycin C	Thymidylate synthase inhibition; DNA cross-linking; bioreductive alkylation	Approved/Inv.	[43]
Pancreatic	Gemcitabine, 5-FU, Oxaliplatin, Irinotecan, Streptozocin	Ribonucleotide reductase inhibition; thymidylate synthase inhibition; DNA alkylation	Approved/Inv.	[44]
Brain Tumours	Temozolomide, Carmustine, Lomustine, Etoposide	DNA methylation/alkylation; topo-II inhibition	Approved/Inv.	[45,46]
Head & Neck	Cisplatin, Bleomycin, 5-FU, Docetaxel, Methotrexate, Mitomycin C	DNA cross-linking; strand scission; thymidylate synthase; DHFR inhibition	Approved/Inv.	[47]

Cervical	Cisplatin, Carboplatin, Topotecan, Ifosfamide, Mitomycin C	DNA cross-linking; topo-I inhibition; DNA alkylation; bioreductive alkylation	Approved/Inv.	[31,48]
Bladder	Cisplatin, Gemcitabine, Thiotepa, Methotrexate, Carboplatin	DNA cross-linking; ribonucleotide reductase inhibition; DNA alkylation; DHFR inhibition	Approved	[49]
Testicular	Bleomycin, Etoposide, Cisplatin (BEP), Ifosfamide, Actinomycin D	DNA strand scission; topo-II inhibition; DNA cross-linking; RNA transcription inhibition	Approved/Inv.	[50]
Prostate	Docetaxel, Mitoxantrone, Ixabepilone	Microtubule stabilisation; topo-II inhibition; tubulin beta-3 inhibition	Approved/Inv.	[51]
Melanoma	Dacarbazine, Temozolomide, Carboplatin/Paclitaxel, Melphalan, Hydroxyurea	DNA cross-linking/methylation; microtubule stabilisation; ribonucleotide reductase inhibition	Approved/Inv.	[34,45]
Neuroblastoma	Cyclophosphamide, Vincristine, Doxorubicin, Etoposide, Carboplatin, Ifosfamide	DNA cross-linking; microtubule inhibition; topo-II inhibition	Approved/Inv.	[26,34]
Wilms Tumour	Actinomycin D, Vincristine, Doxorubicin, Etoposide, Carboplatin	RNA transcription inhibition; microtubule inhibition; topo-II inhibition	Approved/Inv.	[26]
Gestational Trophoblastic	Methotrexate, Actinomycin D, Etoposide, Cyclophosphamide, Vincristine	DHFR inhibition; RNA transcription inhibition; topo-II inhibition; DNA alkylation	Approved	[26]

Abbreviations: DHFR = dihydrofolate reductase; Topo = topoisomerase; Inv. = Investigational; ALL = Acute Lymphoblastic Leukaemia; AML = Acute Myeloid Leukaemia; CLL = Chronic Lymphocytic Leukaemia; CML = Chronic Myelogenous Leukaemia; NSCLC = Non-Small Cell Lung Cancer; SCLC = Small Cell Lung Cancer; BEP = Bleomycin, Etoposide, Cisplatin; ABVD = Doxorubicin, Bleomycin, Vinblastine, Dacarbazine; CRPC = Castration-Resistant Prostate Cancer; HNSCC = Head and Neck Squamous Cell Carcinoma.

3. RECENT ADVANCES IN CANCER THERAPY

Recent advances in cancer therapy have shifted significantly toward a precision medicine framework, focusing on treatments tailored to the specific molecular and genetic profiles of individual tumors. This evolution is characterized by the integration of targeted agents—such as those directed against FLT3, IDH1/2, BCL-2, and menin pathways—into comprehensive management strategies to improve survival outcomes and overcome treatment resistance.[121,125] Modern oncology increasingly leverages these molecular insights to transition from non-specific cytotoxic regimens to highly selective therapies that minimize off-target effects and enhance durable responses.[121]

3.1 Newer and Emerging Anticancer Agents

The landscape of emerging oncology treatments is defined by first-in-class therapies that target previously "undruggable" pathways or bypass common resistance mechanisms. These include non-covalent inhibitors designed to overcome binding site mutations, allosteric inhibitors that stabilize specific protein conformations, and orally bioavailable selective degraders that directly eliminate oncogenic receptors.[116,124] Such innovations, ranging from menin inhibitors for aggressive leukemias to novel selective estrogen receptor degraders for breast cancer, represent a major leap forward in providing effective options for patients with refractory disease.[116,124]

3.2 Overview of Five Breakthrough Anticancer Agents

3.2.1 Elacestrant

Approved by the FDA in 2023, elacestrant is the first orally bioavailable non-steroidal selective estrogen receptor degrader (SERD) indicated for HR-positive, HER2-negative metastatic breast cancer.[116] It is particularly effective for patients with ESR1 mutations, which frequently drive resistance to standard endocrine therapies.[116] Unlike inhibitors that only block signaling, elacestrant binds to and degrades the estrogen receptor to

suppress tumor proliferation and improve progression-free survival.[116,117]

3.2.2 LiPyDau

This next-generation PEGylated liposomal nanoformulation of 2-pyrrolino-daunorubicin (PyDau) was developed to enhance anticancer potency while reducing cardiotoxicity.[118,119] LiPyDau bypasses P-glycoprotein–mediated multidrug resistance and induces irreversible DNA damage through stable interstrand crosslinking.[118,120] Preclinical models have demonstrated its superior efficacy in aggressive tumors, including triple-negative breast cancer and melanoma, compared to standard anthracyclines.[118,120]

3.2.3 Pirtobrutinib (Jaypirca)

Pirtobrutinib is a first-in-class non-covalent Bruton tyrosine kinase (BTK) inhibitor for relapsed or refractory B-cell malignancies like mantle cell lymphoma and CLL.[122] Unlike earlier covalent inhibitors, it binds reversibly to BTK and remains active even in the presence of the C481 mutation, a common cause of drug resistance.[122,123] It offers high bioavailability and a favorable safety profile for heavily pretreated populations.[122,123]

3.2.4 Revumenib

A first-in-class oral menin inhibitor, revumenib targets the interaction between menin and KMT2A fusion proteins in relapsed or refractory acute leukemia.[124,125] By disrupting this bond, it suppresses leukemic gene expression and induces the differentiation of leukemic blasts into normal cells.[124] Clinical trials have shown meaningful responses, including MRD negativity, across both AML and ALL phenotypes.[125]

3.2.5 Asciminib (Scemblix)

Asciminib is a novel therapy for chronic myeloid leukemia (CML) utilizing the STAMP mechanism (Specifically Targeting the ABL Myristoyl Pocket).[126] By binding to an allosteric pocket rather than the traditional ATP-binding site, it achieves high selectivity with fewer off-target effects.[126,127] In clinical trials, it demonstrated superior molecular response rates compared to second-generation TKIs and remains effective against several resistant mutations.[126]

3.3 Advanced Drug Delivery Technologies

3.3.1 Sustained-Release Oral Agents

Sustained-release oral formulations represent a vital advancement by enabling the controlled and prolonged delivery of anticancer drugs, maintaining stable plasma concentrations and reducing toxicity associated with fluctuating drug levels.[114] These systems use polymeric matrices, osmotic pumps, and lipid-based carriers to optimize bioavailability and enable outpatient management.[114] Modern innovations include nanotechnology-based carriers that protect drugs from gastrointestinal degradation and facilitate selective tumor accumulation through the enhanced permeability and retention (EPR) effect.[114,115]

3.3.2 Advanced Liposomal Formulations

Advanced liposomal systems utilize phospholipid vesicles to carry both hydrophilic and lipophilic drugs, significantly improving their pharmacokinetic profiles.[128,129] PEGylated "stealth" liposomes evade immune clearance, leading to prolonged circulation and enhanced tumor retention.[130,131] Modern iterations include ligand-targeted liposomes (e.g., HER2- or PSMA-targeted) and stimuli-responsive "smart" liposomes that release their cargo in response to acidic pH, heat, or ultrasound, thereby maximizing intratumoral concentration while sparing healthy tissue.[132,133]

3.3.3 Immunochemotherapy combinations

Immunochemotherapy combinations integrate cytotoxic drugs with immunotherapeutic agents to produce synergistic effects. Chemotherapy can promote "immunogenic cell death," which increases tumor antigen release and enhances the efficacy of immune checkpoint inhibitors like pembrolizumab or nivolumab.[134,135] One landmark success is the R-CHOP regimen for lymphoma, which revolutionized management by combining a monoclonal antibody with standard chemotherapy.[136] Current research focuses on using biomarkers like PD-L1 expression to personalize these potent combinations.[137]

3.4 Supportive Care and Alternative Chemotherapy Paradigms

3.4.1 Scalp Cooling Therapy

Scalp cooling therapy (SCT) is a primary supportive care strategy used to prevent chemotherapy-induced alopecia (CIA).[138] The technique involves cooling the scalp to induce vasoconstriction and decreased metabolic activity of hair follicles, thereby limiting the uptake of cytotoxic agents.[138,140] Modern automated systems (e.g., Paxman, DigniCap) maintain temperatures between 18°C and 22°C and have shown success rates of 70–90% with taxane-based regimens.[138,139]

3.4.1.1 The Critical Timing of Scalp Cooling

The success of SCT is highly dependent on a rigorous time-based protocol:[126,127]

Pre-infusion: Cooling is initiated approximately 30 minutes before chemotherapy starts to ensure the scalp reaches the protective temperature threshold.

During infusion: The cooling is maintained continuously throughout the entire drug administration period.

Post-infusion: A cooling period follows the infusion, typically ranging from 15 minutes to 4 hours, depending on the specific chemotherapy regimen and drug half-life to ensure follicle protection as plasma levels decline.

3.4.2 Metronomic Chemotherapy/Microdosing Regimen

Metronomic chemotherapy (MCT) is an alternative paradigm where drugs are administered continuously at

low doses without prolonged drug-free intervals.[141] Unlike maximum tolerated dose regimens, MCT targets the tumor microenvironment, focusing on antiangiogenic effects and immune modulation rather than direct cell killing.[141,142] This approach inhibits tumor neovascularization and enhances antitumor immunity by decreasing regulatory T cells, offering a better safety profile and improved quality of life for patients with advanced cancers.[141,143]

4. CONCLUSION

Cancer chemotherapy has evolved significantly from the use of non-specific cytotoxic agents to the development of targeted therapies, immunotherapy, and precision medicine–based approaches. Advances in molecular biology, pharmacogenomics, and tumor immunology have improved the understanding of cancer pathogenesis and enabled the development of therapies that are more selective, effective, and less toxic. Novel anticancer agents such as elacestrant, pirtobrutinib, revumenib, and asciminib, along with innovations in immunochemotherapy, advanced liposomal formulations, and sustained-release drug delivery systems, have transformed modern oncology and improved survival outcomes in several malignancies.

In addition to therapeutic advancements, supportive care strategies such as scalp cooling therapy and alternative treatment paradigms like metronomic chemotherapy have enhanced patient quality of life and treatment tolerability. Despite substantial progress, challenges including multidrug resistance, systemic toxicity, tumor heterogeneity, and high treatment costs continue to limit optimal cancer management. Ongoing research focusing on biomarker-guided therapy, personalized medicine, and next-generation targeted therapeutics is expected to further refine cancer chemotherapy and expand the future scope of precision oncology.

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