Anticancer Agent Effect and Polychemotherapy Regimens for Malignant Tumor Treatment - A Review

Nikolaos Andreas Chrysanthakopoulos1*, Eleftheria Vryzaki2

Abstract
Cancer is a leading cause of millions of deaths worldwide and, despite the improvements in molecular biology, issues concerning how to advance cancer treatment are still relevant. Cancer research must be focused on finding new and efficient chemotherapeutic regimens that can relieve severe side effects caused by conventional treatments. Modern technologies are currently under estimation in clinical trials or have already been introduced into clinical practice. Nowadays cancer therapy is characterized by ineffectiveness and serious side effects, as well as by hope of remission and cure in many cases. Antitumor drugs and radiation have been used as the treatment of choice in some cancer cases, except for the choice of surgery in case of solid tumors. Recently, immunotherapy has emerged as a significant therapeutic alternative, and in many cases, it is the first choice. These therapies can be applied either alone or in combination with other agents. Additionally, gene treatment and nanotechnology are promising methods for cancer treatment as well. The current review presents the progress of cancer treatments, starting with surgery, chemotherapy, radiation and immunotherapy, gene treatment and nanomedicine, giving emphasis to the most common anticancer agents and polychemotherapeutic regimens.

Keywords
Cancer; Polychemotherapy; Side Effects; Anticancer Agents

1 Department of Pathological Anatomy, Medical School University of Athens, Athens, Greece
2 Department of Dermatology, Rio University Hospital of Patras, Greece
*Corresponding author: nchrysant@med.uoa.gr

Introduction
Cancer is a leading cause of millions of deaths worldwide and, despite the improvements in molecular biology, the issues concerning how to advance cancer treatment and to reduce side effects caused by conventional therapies are still relevant.

With cancer progression, malignant tumors become highly heterogeneous, creating a mixed cell population characterized by different molecular features and diverse treatment responsivity. This heterogeneity, that characterizes malignant tumors, is the crucial factor responsible for the development of resistant phenotypes facilitated by selective treatment pressure [1]. Therefore, a deep understanding of these complicated processes is of vital importance to design precise and efficient treatments.

Surgery, radiotherapy, and chemotherapy are the most common cancer treatments available today.

Chemotherapeutic agents are curative in some types of advanced cancer, including acute lymphoblastic leukemia and acute myeloid leukemia (AML), Hodgkin’s and non-Hodgkin’s lymphoma, ovarian cancer, small-cell lung cancer (SCLC), germ cell cancer, and choriocarcinoma, whereas in pediatric patients, curable cancers include acute leukemia, embryonal rhabdomyosarcoma, Wilms’ tumor and Burkitt’s lymphoma [2]. Although chemotherapy regimens are not always effective in various types of cancer, a significant improvement in progression-free and overall survival has been observed. Polychemotherapy regimens are used in various types of malignancies, as they act against malignant cells at different phases of their cell cycle. Many polychemotherapy regimens are used, especially in hematopoietic malignancies [3–5], metastatic germ cancer [6], and breast cancer treatment [7] (Table 1).

Understanding molecular alterations in malignant cells has resulted in many agents with various mechanisms of action. Advances in modern chemotherapy, genetics, and molecular biology have led to the continuing reduction in mortality rates. Genome sequencing studies suggested that many dysfunctions associated with cancer could be attributed to the impaired protein kinase function. Targeted chemotherapy [8], directed against a specific location...
such as tumor vascular system or intracellular organelles, without affecting the adjacent tissues, an observation that increases to a large extent the treatment specificity, eliminates its side effects [9]. Current pharmacological research is focused on developing kinase inhibitors [10], and malignancies targeted by those agents are gastrointestinal stromal tumors, hematopoietic cancer, and renal cell cancer [11]. Various tyrosine kinase inhibitors (TKIs) are used in combination with conventional chemotherapy in specific malignant tumors.

In liposomal cancer treatment, to decrease some side effects of conventional chemotherapy such as cardiotoxicity and myelosuppression, agents are placed inside liposome vesicles constructed from lipid bilayers [12]. Nanomedicine provides conventional chemotherapeutic drugs in vivo, increasing their bioavailability and concentration around tumor tissues, as well as improving their release profile [13].

Recently, extracellular vesicles (EVs) have been widely studied as efficient drug delivery vehicles, as they are involved in cancer development, microenvironment modification and participate in metastatic progression [14].

Another promising method based on gene treatment and gene expression able to trigger apoptosis [15] and wild-type tumor suppressors [16] or the targeted silencing mediated by small interfering RNAs (siRNAs) is currently under investigation in many clinical trials worldwide [17].

Adjuvant chemotherapy is used after surgery or radiotherapy to cure patients with advanced types of cancer, such as breast cancer. It has been effectively applied for many cancers, and with the advent of new effective drugs and drug combinations, the survival rates are expected to increase even more [18].

Neoadjuvant therapy is a cancer treatment method that focuses on reducing primary tumor size and prevents micrometastases. It is indicated for lung cancer, breast cancer, gastrointestinal cancer, anal cancer, rectal cancer, bladder cancer, head and neck cancer, as well as for some sarcoma types and improves more conservative surgical techniques in maintaining important organ functioning [18].

Phytochemical agents and natural antioxidants have recently been suggested as anticancer adjuvants due to their anti-proliferative and pro-apoptotic properties [19].

Another method uses radiolabeled molecules that kill cancer cells by distributing targeted radiation to specific cells containing receptors. Radioactive isotopes (Iodine-125 or Indium-111) release Auger electrons that can be targeted into specific populations of cancer cells, thereby protecting healthy cells [20].

The present research provides a general overview of the most modern chemotherapeutic agents and their combinations applied to treat malignant tumors.

### Historical Background of Chemotherapy

Chemotherapy was introduced at the beginning of the 20th century; however, for treating cancer, it was used only in the 1930s. During the World Wars, soldiers exposed to mustard gas were observed to develop low leukocyte counts – a finding that resulted in the use of nitrogen mustard as the first chemotherapeutic agent to treat lymphomas, a treatment introduced by Gilman in 1943 [21]. In subsequent years, alkylating agents such as chlorambucil and cyclophosphamide were produced to treat cancer [22]. The introduction of methotrexate based on folate antagonists such as aminopterin and amethopterin was used in 1948 for leukemia remission in children [23], whereas in 1951, for treating leukemia, 6-mercaptopurine and 6-thioguanine were developed [24].

Monotherapy drugs were introduced in 1950; however, they resulted in only a short-time response in some cancer types [25], whereas in 1958, choriocarcinoma was first cured with chemotherapy [26]. During the 1960s, hematopoietic cancers were the main targets as there were developed more effective treatments with vincristine and benzylmethylnitrosourea (procarbazine), which were administered to patients with Hodgkin’s disease and leukemia [27].

The MOMP (mitochondrial outer membrane permeabilization) [3] and MOPP (mechlorethamine, vincristine (Oncovin), procarbazine, prednisone) protocols [4] were introduced in 1970 as chemotherapy for patients with advanced Hodgkin’s disease. The same treatment was used for patients with diffuse large B-cell lymphoma and in 1975, there was reported a treatment for advanced diffuse large B-cell lymphoma using the C-MOPP protocol (cyclophosphamide, mechlorethamine, vincristine (Oncovin), procarbazine, prednisone), in which nitrogen mustard was replaced by cyclophosphamide [5]. The combination of vinblastine, cisplatin, and bleomycin resulted in higher treatment rates for metastatic germ cell cancer in 1978 [6]. In addition, CMF (cyclophosphamide, methotrexate, fluorouracil) has been the standard treatment regimen for breast cancer for over 30 years [7] (Table 1). Targeted chemotherapy using drugs to target specific molecules was introduced in 1990 [8], whereas daunorubicin and doxorubicin were the first agents to be applied in nanotechnology-based approaches [12].

Advanced breast cancer was the first type of disease in which positive adjuvant chemotherapy outcomes after surgery or radiotherapy were recorded. In the late 1960s, the use of adjuvant chemotherapy changed the concept of localized treatment [18].

### Chemotherapeutic Agents Used in Malignant Tumor Treatment

Basic chemotherapeutic agents are divided into the following categories: cytotoxic medications with different mechanisms of action such as antimetabolites that inhibit or alter one or more of the metabolic reactions involved in DNA synthesis; alkylating agents and their derivatives that act by forming covalent bonds with DNA, thereby inhibiting its replication; cytotoxic antibiotics - agents produced by microorganisms that prevent cell division in mammals; plant derivatives that have a specific effect on the formation of microtubules and, therefore, the formation of the mitotic spindle; hormones and agents that suppress hormone secretion or compete with their action; various agents that do not fall into any of the previous categories and belong to drugs focusing on specific targets [25].
**Table 1. Combinations of anticancer chemotherapeutic agents.**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Ingredients</th>
<th>Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD [68]</td>
<td>Doxorubicin, bleomycin, vinblastine, dacarbazine (DTIC)</td>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>AC [69]</td>
<td>Doxorubicin, cyclophosphamide</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>BACO [70]</td>
<td>Bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>BEACOPP [71]</td>
<td>Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone</td>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>BEAM [72]</td>
<td>Carmustine, etoposide, cytarabine, melphalan</td>
<td>Hodgkin’s and non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>BEP [73]</td>
<td>Bleomycin, etoposide, cisplatin</td>
<td>Testicular cancer, germ cell tumors</td>
</tr>
<tr>
<td>VCD [74]</td>
<td>Bortezomib, cyclophosphamide, dexamethasone</td>
<td>Myeloma</td>
</tr>
<tr>
<td>VMP [75]</td>
<td>Bortezomib, melphalan, prednisolone</td>
<td>Myeloma</td>
</tr>
<tr>
<td>VTD [76]</td>
<td>Bortezomib, thalidomide, dexamethasone</td>
<td>Myeloma</td>
</tr>
<tr>
<td>XELOX [77]</td>
<td>Oxaliplatin, capcitabine</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>CAV [78]</td>
<td>Cyclophosphamide, doxorubicin, vincristine</td>
<td>SCLC</td>
</tr>
<tr>
<td>CAF [79]</td>
<td>Cyclophosphamide, doxorubicin, fluorouracil</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>CEPP [80]</td>
<td>Cyclophosphamide, etoposide, procarbazine, prednisone</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>CHOP [81]</td>
<td>Cyclophosphamide, doxorubicin, vincristine, prednisolone</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>CMF [83]</td>
<td>Cyclophosphamide, methotrexate, fluorouracil</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>CMV [84]</td>
<td>Cisplatin, methotrexate, vinblastine</td>
<td>Bladder cancer</td>
</tr>
<tr>
<td>COPP [85]</td>
<td>Cyclophosphamide, vincristine, procarbazine, prednisone</td>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>CVE [86]</td>
<td>Carboplatin, vincristine, etoposide</td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>CVP [81]</td>
<td>Cyclophosphamide, vincristine, prednisolone</td>
<td>Low-grade non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>PC [87]</td>
<td>Paclitaxel, carboplatin</td>
<td>Different cancer types</td>
</tr>
<tr>
<td>CD [88]</td>
<td>Carfilzomib, dexamethasone</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>ChIVPP [89]</td>
<td>Chlorambucil, vinblastine, procarbazine, prednisolone</td>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>CX [90]</td>
<td>Cisplatin, capectabine</td>
<td>Gastric and GOJ cancer</td>
</tr>
<tr>
<td>CSFU [91]</td>
<td>Cisplatin, fluorouracil</td>
<td>Anal cancer, head and neck cancer, esophageal cancer</td>
</tr>
<tr>
<td>VIP [92]</td>
<td>Cisplatin, etoposide, ifosfamide</td>
<td>Testicular cancer, metastatic or relapsed</td>
</tr>
<tr>
<td>CSFUT [93]</td>
<td>Cisplatin, fluorouracil, trastuzumab</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>CTD [94]</td>
<td>Cyclophosphamide, thalidomide, dexamethasone</td>
<td>Myeloma</td>
</tr>
<tr>
<td>DAT [95]</td>
<td>Daunorubicin, cytarabine, tioguanine</td>
<td>AML</td>
</tr>
<tr>
<td>DHAP [96]</td>
<td>Dexamethasone, cytarabine, cisplatin</td>
<td>Non-Hodgkin’s and Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>DICE [97]</td>
<td>Dexamethasone, ifosfamide, cisplatin, etoposide</td>
<td>Aggressive relapsed lymphomas, progressive neuroblastoma</td>
</tr>
<tr>
<td>DT [98, 99]</td>
<td>Dabrafenib, trametinib</td>
<td>Skin melanoma, NSCLC</td>
</tr>
<tr>
<td>TPF [100]</td>
<td>Docetaxel, cisplatin, fluorouracil</td>
<td>Head and neck cancer</td>
</tr>
<tr>
<td>Doxifos [101]</td>
<td>Doxorubicin, ifosfamide</td>
<td>Soft tissue sarcoma</td>
</tr>
<tr>
<td>EC [102]</td>
<td>Epirubicin, cyclophosphamide</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>ECF [103]</td>
<td>Epirubicin, cisplatin, fluorouracil</td>
<td>Gastric and esophagus cancer</td>
</tr>
<tr>
<td>EOF [104]</td>
<td>Epirubicin, oxaliplatin, fluorouracil</td>
<td>Gastric, esophageal, and GOJ cancer</td>
</tr>
<tr>
<td>EOX [105]</td>
<td>Epirubicin, oxaliplatin, capecitabine</td>
<td>Esophageal and gastric cancer</td>
</tr>
<tr>
<td>EP [91]</td>
<td>Etoposide, cisplatin</td>
<td>Different cancer types</td>
</tr>
<tr>
<td>EPOCH [106]</td>
<td>Etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin</td>
<td>non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>ESHAP [107]</td>
<td>Etoposide, methylprednisolone, cytarabine, cisplatin</td>
<td>Hodgkin’s and non-Hodgkin’s lymphoma, myeloma</td>
</tr>
<tr>
<td>EB [108]</td>
<td>Encorafenib, binimetinib</td>
<td>Skin melanoma</td>
</tr>
<tr>
<td>ECX [109]</td>
<td>Epirubicin, cisplatin, capectabine</td>
<td>Gastric, esophageal, GOJ cancer</td>
</tr>
<tr>
<td>FAM [110]</td>
<td>Fluorouracil, doxorubicin, mitomycin C</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>FEC [111]</td>
<td>Fluorouracil, epirubicin, cyclophosphamide</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>FLOT [112]</td>
<td>Fluorouracil, leucovorin, oxaliplatin, docetaxel</td>
<td>Gastric, esophageal, GOJ cancer</td>
</tr>
<tr>
<td>FMD [113]</td>
<td>Fludarabine, mitoxantrone, dexamethasone</td>
<td>Non-Hodgkin’s lymphoma, chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>FOLFIRINOX [114]</td>
<td>Leucovorin, fluorouracil, irinotecan, oxaliplatin</td>
<td>Advanced pancreatic cancer</td>
</tr>
<tr>
<td>FCR [115]</td>
<td>Fludarabine, cyclophosphamide, rituximab</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>F5UMC [116]</td>
<td>Fluorouracil, mitomycin C</td>
<td>Anal, vulva, bladder cancer</td>
</tr>
<tr>
<td>FECT’ [117]</td>
<td>Fluorouracil, epirubicin, cyclophosphamide, docetaxel</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>FOLFIRI [118]</td>
<td>Leucovorin, fluorouracil, irinotecan</td>
<td>Advanced colorectal, other digestive (gastric) cancers</td>
</tr>
</tbody>
</table>
### A - Alkylating Agents and Their Derivatives

The principal effect of alkylating agents is apoptosis and cell death. They are used in several types of cancer such as Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, glioblastoma multiforme, anaplastic astrocytoma, leukemia, ovarian cancer, multiple myeloma, melanoma, chronic myeloid leukemia, chronic lymphocytic leukemia, etc. [28].

Alkylating agents are responsible for myelosuppression and gastrointestinal tract disorders. After prolonged use of these agents, a disruption of gametogenesis, especially in males, with subsequent infertility, as well as an increased risk of acute non-lymphoblastic leukemia and other malignancies have been recorded [29]. Nitrogen mustards, nitrosoureas, alkyl sulfonates, triazines, and ethylenimines belong to this category.

The most commonly used nitrogen mustard is cyclophosphamide which has a strong effect on lymphocytes and can be used as an immunosuppressive agent. Other agents in this category are mechlorethamine and melphalan [25]. Toxic effects, including nausea and vomiting, myelosuppression and hemorrhagic cystitis, have been observed [30].

Nitrosoureas includes the chloroethyl nitrosoureas loxostine and carmustine, lipid-soluble substances that can cross the blood-brain barrier and are used to treat brain and meningeal malignancies. Other agents in this category include streptozotocin, photemustine and semustine. Most nitrosoureas have a pronounced cumulative suppressive effect on the bone marrow, which begins to manifest itself
three-six weeks after starting treatment [31].

Alkylsulfonates have a selective effect on the bone marrow; in low doses, they suppress the formation of granulocytes and platelets, while in high doses, they prevent the formation of erythrocytes. In addition, they have little to no effect on the gastrointestinal tract and lymphatic tissue. Busulfan is the representative agent in the class of alkylsulfonates [25].

Dacarbazine is the most commonly used agent in the triazine category. Its side effects include myelotoxicity and severe nausea and vomiting. Another agent in this category is temozolomide [32].

Ethylidenamines are another category containing thiotapec and hexamethylmelamine. The platinum-based anticancer drugs (cisplatin, carboplatin and oxalaplatin) fall into this category as well, as they destroy cancer cells in a similar way [19]. The action of cisplatin is similar to that of alkylating agents [19, 33]. It is extremely nephrotoxic, has low myelotoxicity, and causes severe nausea and vomiting. 5-HT3 (serotonin) antagonists such as ondansetron are very effective in preventing nausea and vomiting and have significantly improved chemotherapy with this agent. High concentrations may result in tinnitus and hearing loss, as well as peripheral neuropathy, hyperuricemia, and anaphylactic reactions. Carboplatin, a derivative of cisplatin, is less nephrotoxic, neurotoxic, and ototoxic causing milder nausea and vomiting than cisplatin; however, it is more myelotoxic [33].

Procarbazine is mainly used in Hodgkin’s disease. It interacts with other drugs, causes a disulfiram-like reaction when co-administered with alcohol, exacerbates central nervous system (CNS) depressants, and, being a weak monoamine oxidase inhibitor, it may cause hypertension if co-administered with certain sympathomimetic drugs. Its side effects are typical for anticancer drugs, furthermore, it is myelotoxicity and mild myelosuppression; however, it is more myelotoxic [33].

B - Antimetabolites
This category includes folic acid antagonists, pyrimidine, and purine analogues. They are used in gastric cancer, oesophageal cancer, pancreatic cancer, cervical cancer, testicular cancer, ovarian cancer, colorectal cancer, non-small-cell lung cancer (NSCLC), bladder cancer, breast cancer, B-cell chronic lymphocytic leukemia, relapsed or refractory acute lymphoblastic leukemia, AML and acute lymphoblastic leukemia, chronic myeloid leukemia, non-Hodgkin’s lymphoma, etc. [35].

The most important folic acid antagonist is methotrexate, one of the most commonly used antimetabolites in cancer chemotherapy. Cancer cells can develop methotrexate resistance due to several mechanisms [19, 36]. Side effects are myelosuppression and destruction of the gastrointestinal epithelium. Pneumonitis can be observed, while high doses can cause nephrotoxicity due to the deposition of the drug or some of its metabolites in the renal tubules [36].

Hydroxyamidamide (hydroxyurea) is a ura analogue and has typical side effects, with myelosuppression as the most common one [37]. It is used in chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, AML, and cervical cancer.

Fluorouracil (5-FU) is a pyrimidine analogue of uracil. The most important side effects relate to the gastrointestinal epithelium and myelotoxicity; cerebellar disorders can be observed as well [38].

Cytarabine is a 2'-deoxyctydine nucleoside analogue. The most common side effects are myelotoxicity, nausea, and vomiting [39]. Gemcitabine is a promising cytarabine analogue that has fewer side effects, as it causes a flu-like illness and mild myelotoxicity. Capecitabine is another drug in this subcategory [40].

Purine analogues include fludarabine, pentostatin, cladribine, mercaptapurine, and thioguanine. Fludarabine causes myelosuppression [19]. Pentostatin has a different mechanism of action [41], whereas azacytidine is a cytidine chemical analogue and has an antineoplastic effect causing hypomethylation of DNA, and high doses result in a direct cytotoxicity to malignant cells [42].

C - Cytotoxic Antibiotics
This category contains anthracyclines and other anticancer antibiotics such as actinomycin-D, bleomycin, mithramycin and mitomycin-C.

The most important anthracyclines are doxorubicin, epirubicin, mitoxantrone, idarubicin, aclarubicin, and daunorubicin. They are used to treat Kaposi’s sarcoma, AML and lymphoblastic leukemia, chronic myeloid leukemia, breast cancer, ovarian cancer, other solid tumors and different types of cancer [19].

Doxorubicin causes a variety of side effects including myelotoxicity, damage to the epithelium of the gastrointestinal tract and, in addition, can cause a cumulative dose-dependent cardiotoxicity resulting in arrhythmias and heart failure [34]. Epirubicin and mitoxantrone have the structure similar to that of doxorubicin. Mitoxantrone causes dose-dependent cardiotoxicity and myelosuppression, while epirubicin is less cardiotoxic than doxorubicin [43].

Actinomycin D may have common side effects of chemotherapy agents and is used in Wilms tumor, rhabdomyosarcoma, Ewing’s sarcoma, trophoblastic neoplasm, testicular cancer, certain types of ovarian cancer [44].

Bleomycins are a group of metallo-glycopeptide antibiotics used in Hodgkin’s and non-Hodgkin’s lymphoma, testicular cancer, ovarian cancer, and cervical cancer. They cause mild myelosuppression; however, their most severe toxic effect is pulmonary fibrosis that is observed in 10% of patients, with fatal outcomes in 1% of cases. Allergic reactions can develop in 50% of patients and involve skin reactions and mucosal reactions [45]. Mitomycin causes severe myelosuppression, can cause kidney damage and pulmonary fibrosis and is used in esophageal carcinoma, anal cancer, and breast cancer [46].

D - Mitotic Inhibitors
This category contains agents that are often plant derivatives and includes taxanes (paclitaxel, docetaxel), epothilo-
Tumors arising from hormone-sensitive cells may be hormonally dependent and their development can be inhibited by hormones with the opposite effect, by hormone antagonists, or by agents inhibiting hormone synthesis and secretion. Hormones and hormone analogues having an inhibitory effect on certain tissues can be used to treat tumors originating in these tissues [19, 53]. This category contains glucocorticoids [53], estrogens [19, 53], progestogens such as megestrol, and medroxyprogesterone [19]. Gonadotropins releasing hormone analogues such as goserelin [53] and hormone antagonists such as tamoxifen have a cardioprotective effect partly because of its ability to protect low-density lipoproteins (LDL) from oxidation [54].

Steroidal antiandrogens such as flutamide and cyproterone are used in prostate tumors [53]. Formestane acts at the advanced stage of sex hormone synthesis. They are used in breast cancer, prostate cancer, endometrial cancer, carcinoid syndrome, vipomas, and advanced neuroendocrine tumors (NETs) [53].

Trilostane and aminogluthethimide also inhibit sex hormone synthesis at the early stage. When used, corticosteroid replacement therapy is required [55].

G - Molecularly-Targeted Treatment
Monoclonal antibodies and small molecules are the main categories of targeted therapy. Targeted therapy uses agents to target specific genes and proteins that are involved in cancer cell development and survival [56].

Monoclonal antibodies are immunoglobulins produced by cell culture that selected to specifically react with antigens expressed by cancer cells [53].

This category contains the following monoclonal antibodies: alemtuzumab, bevacizumab, cetuximab, gemtuzumab ozogamicin, ipilimumab, nivolumab, ofatumumab, panitumumab, pembrolizumab, ranibizumab, rituximab, and trastuzumab [56, 57].

They are used in chronic lymphocytic leukemia, follicular lymphoma, advanced colorectal cancer, NSCLC, skin melanoma, early and advanced breast cancer (neoadjuvant treatment, adjuvant treatment, secondary or recurrent breast cancer), advanced gastric and cervical cancer, etc., and in combination with conventional anticancer agents [57] (Table 1). Side effects of rituximab include hypotension, fever, and chills during the initial infusion and hypersensitivity reactions following administration. A cytokine release syndrome may be observed, which in some cases can be fatal. It can also worsen preexisting cardiovascular problems [58]. Side effects of trastuzumab are similar to the previous agent [59].

Small molecules include TKIs [60]. These molecules are able to target the epidermal growth factor receptor (EGFR), act as an apoptosis-inducing proteasome inhibitor, Janus kinase inhibitors, ALK (anaplastic lymphoma kinase) inhibitors, BCL-2 (B-cell lymphoma 2) inhibitors, PARP (poly adenosine diphosphate-ribose polymerase) inhibitors, PI3K (phosphoinositide 3-kinase) inhibitors, BRAF inhibitors, MEK inhibitors, CDK (cyclin-dependent kinase) inhibitors, etc. [61–63].

This category includes imatinib, gefitinib, erlotinib, sorafenib, sunitinib, dasatinib, nilotinib, bortezomib, tofacitinib, crizotinib, olaparib, rucaparib, niraparib, talazoparib, vemurafenib, dabrafenib, trametinib, etc. [62, 64].

They are used in advanced hepatocellular carcinoma, advanced renal cancer, certain types of thyroid cancer, early stage breast cancer, relapsed or metastatic chronic myeloid leukemia, lung adenocarcinoma (recurrent or metastatic), peritoneal cancer, ovarian cancer, metastatic or advanced breast cancer, some types of advanced soft tissue sarcomas, cholangiocarcinoma, etc. [61]. Moreover, those molecules can be used in combination with conventional chemotherapeutic agents (Table 1).

Imatinib mesylate causes vomiting, diarrhea, muscle pain, headache, and rash, while severe side effects may include fluid retention, gastrointestinal bleeding, bone marrow suppression, liver problems, and heart failure [65].
H - Various Chemotherapeutic Agents

Crisantaspase is obtained from Erwinia chrysanthemi and is used in the treatment of acute lymphoblastic leukemia. It causes very mild myelosuppression and has very little effect on the gastrointestinal mucosa or hair follicles. In addition, it results in nausea and vomiting, and may lead to CNS depression, anaphylactic reactions, and liver damage [64].

Mitotane is a steroidogenesis inhibitor and cytostatic antineoplastic medication used exclusively in adrenocortical carcinoma [66]. It causes anorexia, nausea, diarrhea, vomiting, decreased memory and ability to concentrate, rash, gynecomastia, arthralgia, and leukopenia [67].

Conclusions

It is obvious that chemotherapy administered for treating malignant tumors is constantly evolving. Nowadays the number of anticancer drugs and their combinations for the treatment of all solid and hematological tumors has increased, which has contributed to a significant reduction in cancer mortality rates.

Ethical Statement & Informed Consent

Not applicable.

Conflict of Interest

The authors declare that no conflicts exist.

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