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

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, hepatocellular 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 metastasis progression [14].

Another promising method based on gene treatment and gene expression ability 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, gastroesophageal 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 vinca alkaloids and benzimidazoles (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 vindesine, 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.

| Medication | Ingredients | Indication(s) |
|------------|-------------|---------------|
| ABVD [68]  | Doxorubicin, bleomycin, vinblastine, dacarbazine (DTIC) | Hodgkin’s lymphoma |
| AC [69]    | Doxorubicin, cyclophosphamide | Breast cancer |
| BACO [70]  | Bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone | Non-Hodgkin’s lymphoma |
| BEACOPP [71] | Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone | Hodgkin’s lymphoma |
| BEAM [72]  | Carmustine, etoposide, cytarabine, melphalan | Hodgkin’s and non-Hodgkin’s lymphoma |
| BEP [73]   | Bleomycin, etoposide, cisplatin | Testicular cancer, germ cell tumors |
| VCD [74]   | Bortezomib, cyclophosphamide, dexamethasone | Myeloma |
| VMP [75]   | Bortezomib, melphalan, prednisolone | Myeloma |
| VTD [76]   | Bortezomib, thalidomide, dexamethasone | Myeloma |
| XELOX [77] | Oxaliplatin, capecitabine | Colorectal cancer |
| CA V [78]  | Cyclophosphamide, doxorubicin, vincristine | SCLC |
| CAM [79]   | Cyclophosphamide, doxorubicin, fluorouracil | Breast cancer |
| CEP [80]   | Cyclophosphamide, etoposide, procarbazine, prednisone | Non-Hodgkin’s lymphoma |
| CHOP [81]  | Cyclophosphamide, doxorubicin, vincristine, prednisolone | Non-Hodgkin’s lymphoma |
| CHOP [81]  | Cyclophosphamide, etoposide, procarbazine, prednisone | Non-Hodgkin’s lymphoma |
| CMF [83]   | Cyclophosphamide, methotrexate, fluorouracil | Breast cancer |
| CMV [84]   | Cisplatin, methotrexate, vinblatistine | Bladder cancer |
| COPP [85]  | Cyclophosphamide, vincristine, procarbazine, prednisone | Hodgkin’s lymphoma |
| CVE [86]   | Carboplatin, vincristine, etoposide | Retinoblastoma |
| CVP [81]   | Cyclophosphamide, vincristine, prednisolone | Low-grade non-Hodgkin’s lymphoma |
| PC [87]    | Paclitaxel, carboplatin | Different cancer types |
| CD [88]    | Carfilzomib, dexamethasone | Multiple myeloma |
| ChIVPP [89] | Chlorambucil, vinblastine, procarbazine, prednisolone | Hodgkin’s lymphoma |
| CX [90]    | Cisplatin, capecitabine | Gastric and GOJ cancer |
| CFU [91]   | Cisplatin, fluorouracil | Anal cancer, head and neck cancer, esophageal cancer |
| VIP [92]   | Cisplatin, etoposide, ifosfamide | Testicular cancer, metastatic or relapsed |
| CSFUT [93] | Cisplatin, fluorouracil, trastuzumab | Gastric cancer |
| CTD [94]   | Cyclophosphamide, thalidomide, dexamethasone | Myeloma |
| DAT [95]   | Daunorubicin, cytarabine, tioguanine | AML |
| DHAP [96]  | Dexamethasone, cytarabine, cisplatin | Non-Hodgkin’s and Hodgkin’s lymphoma |
| DICE [97]  | Dexamethasone, ifosfamide, cisplatin, etoposide | Aggressive relapsed lymphomas, progressive neuroblastoma |
| DT [98, 99]| Dabrafenib, trametinib | Skin melanoma, NSCLC |
| TPF [100]  | Docetaxel, cisplatin, fluorouracil. | Head and neck cancer |
| Doxxifos [101] | Doxorubicin, ifosfamide | Soft tissue sarcoma |
| EC [102]   | Epirubicin, cyclophosphamide | Breast cancer |
| ECF [103]  | Epirubicin, cisplatin, fluorouracil | Gastric and esophagus cancer |
| EOF [104]  | Epirubicin, oxaliplatin, fluorouracil | Gastric, esophageal, and GOJ cancer |
| EOX [105]  | Epirubicin, oxaliplatin, capecitabine | Esophageal and gastric cancer |
| EP [91]    | Etoposide, cisplatin | Different cancer types |
| EPOCH [106] | Etoposide, prednisone, vincristine, cyclophosphamide, hydroxydaunorubicin | non-Hodgkin’s lymphoma |
| ESHAP [107] | Etoposide, methylprednisolone, cytarabine, cisplatin | Hodgkin’s and non-Hodgkin’s lymphoma, myeloma |
| EB [108]   | Encorafenib, binimetinib | Skin melanoma |
| ECX [109]  | Epirubicin, cisplatin, capecitabine | Gastric, esophageal, GOJ cancer |
| FAM [110]  | Fluorouracil, doxorubicin, mitomycin C | Gastric cancer |
| FEC [111]  | Fluorouracil, epirubicin, cyclophosphamide | Breast cancer |
| FLOT [112] | Fluorouracil, leucovorin, oxaliplatin, docetaxel | Gastric, esophageal, GOJ cancer |
| FMD [113]  | Fluorouracil, mitoxantrone, dexamethasone | Non-Hodgkin’s lymphoma, chronic lymphocytic leukemia |
| FOLFRINOX [114] | Leucovorin, fluorouracil, irinotecan, oxaliplatin | Advanced pancreatic cancer |
| FCR [115]  | Fluorouracil, cyclophosphamide, rituximab | Chronic lymphocytic leukemia |
| F5UMC [116] | Fluorouracil, mitomycin C | Anal, vulva, bladder cancer |
| FEC-T [117] | Fluorouracil, epirubicin, cyclophosphamide, docetaxel | Breast cancer |
| FOLFIRI [118] | Leucovorin, fluorouracil, irinotecan | Advanced colorectal, other digestive (gastrointestinal) cancers |
### Medication Ingredients Indication(s)

| Medication | Ingredients | Indication(s) |
|------------|-------------|---------------|
| FOLFOX [119] | Leucovorin, fluorouracil, oxaliplatin | Colorectal cancer |
| FOLFOXIRI [120] | Leucovorin, fluorouracil, oxaliplatin, irinotecan | Colorectal cancer |
| GemCap [121] | Gemcitabine, capectabine | Pancreatic cancer |
| GC [122–124] | Gemcitabine, cisplatin | Urothelial, biliary tract, NSCLC |
| GDC [125] | Gemtuzumab ozogamicin, daunorubicin and cytarabine | AML |
| ICE [126] | Ifofamide, carboplatin, etoposide | Hodgkin’s and non-Hodgkin’s lymphoma |
| PEI [127] | Cisplatin, etoposide, ifosfamide | Testicular cancer |
| IN [128] | Iplimunab, nivolumab | Advanced skin melanoma, advanced kidney cancer |
| CAPRI [129] | Irinotecan, capecitabine | Metastatic colorectal cancer |
| ILD [130] | Irinotecan, oxaliplatin, leucovorin | Myeloma |
| MMM [131] | Mitoxantrone, mitomycin C, methotrexate | Breast cancer |
| MVAC [132] | Methotrexate, vinblastine, doxorubicin, cisplatin | Bladder cancer |
| MPT [133] | Melphalan, prednisolone, thalidomide | Myeloma |
| MDC [134] | Midostaurin, daunorubicin, cytarabine | AML |
| NP [135] | Cisplatin, vinorelbin | NSCLC |
| PMitCEBO [136] | Prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine | Non-Hodgkin’s lymphoma, some other cancer types |
| POMB/ACE [137] | Cisplatin, vinristine, methotrexate, bleomycin, dactinomycin, cyclophosphamide, etoposide | Germ cell tumors |
| PBD [138] | Panobinostat, bortezomib, dexamethason | Myeloma |
| PECAR [139] | Pemetrexed, carboplatin | NSCLC, mesothelioma |
| RECIS [140] | Pemetrexed, cisplatin | NSCLC, mesothelioma |
| PD [141] | Pomalidomide, dexamethasone | Refractory/relapsed myeloma |
| PCV [142] | Procarbazine, lomustine, vincristine | Glioma |
| R-CHOP [143] | Rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisolone | Non-Hodgkin’s lymphoma, nodular lymphocyte predominant Hodgkin’s lymphoma |
| R-CVP [144] | Rituximab, cyclophosphamide, vincristine, prednisolone | Low-grade non-Hodgkin’s lymphoma |
| R-DHAP [145] | Rituximab, dexamethasone, cytarabine, cisplatin | High-grade non-Hodgkin’s lymphoma |
| R-ESHAP [146] | Rituximab, etoposide, methylprednisolone, cytarabine, cisplatin | Lymphomas |
| R-GCVP [147] | Rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone | B-cell lymphomas |
| RICE [148] | Rituximab, ifosfamide, carboplatin, etoposide | Non-Hodgkin’s lymphoma, relapsed Hodgkin’s lymphoma |
| TAC [149] | Docetaxel, doxorubicin, cyclophosphamide | Breast cancer |
| TIP [150] | Paclitaxel, ifosfamide, cisplatin | Testicular cancer |
| TC [151] | Docetaxel, cyclophosphamide | Breast cancer |
| TP [152] | Trastuzumab, pertuzumab | Breast cancer |
| VDE [153] | Vinristine, ifosfamide, doxorubicin, etoposide | Ewing’s sarcoma |
| VeIP [154] | Vinblastine, ifosfamide, cisplatin | Testicular cancer |
| VAC [155] | Vincristine, dactinomycin, cyclophosphamide | Ewing’s sarcoma |
| VAI [156] | Vincristine, dactinomycin, ifosfamide | Ewing’s sarcoma |
| VAD [157] | Vincristine, doxorubicin, dexamethasone | Multiple myeloma |

**Notes:** NSCLC – non-small-cell lung cancer; SCLC – small-cell lung cancer; AML – acute myeloid leukemia; GOJ – gastro-esophageal junction.

### 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 chloroethylnitrosoureas lomustine 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...
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 temozolamide [32].

Ethylidenines 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. Carboxanp, 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 can cause carcinogenesis, teratogenicity, and leukemia. If an allergic skin reaction occurs, the drug may be discontinued [34].

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 lymphocytic 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].

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

Fluorouracil (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, aclacinomycin, 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 chemotherapeutic 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]. Gonadotropin-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].

Fornestane 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 aminoglutethimide 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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**References**

[1] Dagogo-Jack I, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. Nature Reviews Clinical Oncology. 2017;15(2):81–94. Available from: https://doi.org/10.1038/nrclinonc.2017.166

[2] Savage P. Clinical observations on chemotherapy curable malignancies: unique genetic events, frozen development and enduring apoptotic potential. BMC Cancer. 2015;15(1):11. Available from: https://doi.org/10.1186/s12885-015-1006-6

[3] Moxley JH, De Vita VT, Brace K, Frei E. III Intensive combination chemotherapy and X-irradiation in Hodgkin’s disease. Cancer Res. 1967;27:1258-1263.

[4] Devita VT. Combination chemotherapy in the treatment of advanced Hodgkin’s disease. Annals of Internal Medicine. 1970;73(6):881-895. Available from: https://doi.org/10.7326/0003-4819-73-6-881

[5] Devita VT, Canellos GP, Chabner B, Schein P, Hubbard SP, Young RC. Advanced diffuse histiocytic lymphoma, a potentially curable disease. The Lancet. 1975;305(7901):248–50. Available from: https://doi.org/10.1016/S0140-6736(75)91142-3

[6] Einhorn LH. cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Annals of Internal Medicine. 1977;87(3):293-298. Available from: https://doi.org/10.7326/0003-4819-87-3-293

[7] Anders CK, Johnson R, Litton J, Phillips M, Bleyer A. Breast cancer before age 40 years. Seminars in Oncology. 2009;36(3):237–249. Available from: https://doi.org/10.1053/j.seminoncol.2009.03.001

[8] Bhullar KS, Lagarón NO, McGowan EM, Parmar I, Jha A, Hubbard BP, et al. Kinase-targeted cancer therapies: progress, challenges and future directions. Molecular Cancer. 2018;17(1):48. Available from: https://doi.org/10.1186/s12943-018-0804-2

[9] Bazak R, Houri M, El Achy S, Kamel S, Refaat T. Cancer active targeting by nanoparticles: a comprehensive review of literature. Journal of Cancer Research and Clinical Oncology. 2014;141(5):769–784. Available from: https://doi.org/10.1007/s00432-014-1767-3

[10] Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. New England Journal of Medicine. 2005;353(2):172–187. Available from: https://doi.org/10.1056/NEJMra044389

[11] Kim A, Balis FM, Widemann BC. Sorafenib and sunitinib. The Oncologist. 2009;14(8):800–805. Available from: https://doi.org/10.1634/theoncologist.2009-0088

[12] Hofheinz R-D, Gnad-Vogt SU, Beyer U, Hochhaus A. Liposomal encapsulated anti-cancer drugs. Anti-Cancer Drugs. 2005;16(7):691–707. Available from: https://doi.org/10.1097/01.cad.0000167902.53039.5a

[13] Martinelli C, Pucci C, Ciofani G. Nanostructured carriers as innovative tools for cancer diagnosis and therapy. APL Bioengineering. 2019;3(1):011502. Available from: https://doi.org/10.1063/1.5079943

[14] Kumar B, Garcia M, Murakami JL, Chen C-C. Exosome-mediated microenvironment dysregulation in leukemia. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 2016;1863(3):464–470. Available from: https://doi.org/10.1016/j.bbamcr.2015.09.017

[15] Lebedeva IV, Su Z-Z, Sarkar D, Fisher PB. Restoring apoptosis as a strategy for cancer gene therapy: focus on p53 and mdm-7. Seminars in Cancer Biology. 2003;13(2):169–178. Available from: https://doi.org/10.1016/S1044-579X(02)00134-7

[16] Shanker M, Jin J, Branch CD, Miyamoto S, Grimm EA, Roth JA, et al. Tumor suppressor gene-based nanotherapy: from test tube to the clinic. Journal of Drug Delivery. 2011;2011:1–10. Available from: https://doi.org/10.1155/2011/465845
[39] Chhikara BS, Parang K. Development of cytarabine prodrugs and delivery systems for leukemia treatment. Expert opinion on drug delivery. 2010;7(12):1399–1414. Available from: https://doi.org/10.1517/17425247.2010.527330

[40] Birhanu G, Javar HA, Seyedjafari E, Zandi-Karimi A. Nanotechnology for delivery of gemcitabine to treat pancreatic cancer. Biomedicine & Pharmacotherapy. 2017;88:635–643. Available from: https://doi.org/10.1016/j.biopharma.2017.01.071

[41] Sahasranaman S, Howard D, Roy S. Clinical pharmacology and pharmacogenetics of thiopurines. European Journal of Clinical Pharmacology. 2008;64(8):753–67. Available from: https://doi.org/10.1007/s00228-008-0478-6

[42] Estey EH. Epigenetics in clinical practice: the examples of azacitidine and decitabine in myelodysplasia and acute myeloid leukemia. Leukemia. 2013;27(9):1803–1812. Available from: https://doi.org/10.1038/leu.2013.173

[43] Koeller J, Ebbe M. Mitoxantrone: a novel anthracycline derivative. Clin Pharm. 1988;7(8):574-581.

[44] Sobell HM. Actinomycin and DNA transcription. Proceedings of the National Academy of Sciences. 1985;82(16):5328–31. Available from: https://doi.org/10.1073/pnas.82.16.5328

[45] Dorr RT. Bleomycin pharmacology: mechanism of action and resistance, and clinical pharmacokinetics. Semin Oncol. 1992;19(2 Suppl 5):3-8.

[46] Verweij J, Pinedo HM. Mitomycin C. Anti-cancer drugs. 1990;1(1):5–14. Available from: https://doi.org/10.1097/00001813-199010000-00002

[47] Sears JE, Boger DL. Total Synthesis of vinblastine, related natural products, and key analogues and development of inspired methodology suitable for the systematic study of their structure–function properties. Accounts of Chemical Research. 2015;48(3):653–662. Available from: https://doi.org/10.1021/ar500400w

[48] Keglevich P, Hazai L, Kalaus G, Szántay C. Modifications on the basic skeletons of vinblastine and vincristine. Molecules. 2012;17(5):5893–5914. Available from: https://doi.org/10.3390/molecules17055893

[49] Weaver BA. How taxol/paclitaxel kills cancer cells. Bement W, editor. Molecular Biology of the Cell. 2014;25(18):2677–2681. Available from: https://doi.org/10.1017/mbc.e14-04-0916

[50] Delgado JL, Hsieh C-M, Chan N-L, Hsia H. Topoisomerases as anticancer targets. Biochemical Journal. 2018;475(2):373–398. Available from: https://doi.org/10.1042/BCJ20160583

[51] Wall ME. Camptothecin and taxol: discovery to clinic. Medicinal Research Reviews. 1998;18(5):299–314. Available from: https://doi.org/10.1002/(SICI)1098-1128(199809)18:5:299::AID-MED23.0.CO;2-O

[52] Cragg GM, Newman DJ. Plants as a source of anti-cancer agents. Journal of Ethnopharmacology. 2005;100(1–2):72–79. Available from: https://doi.org/10.1016/j.jep.2005.05.011

[53] DeVita VT, Hellman A, Rosenberg SA, eds. Cancer: principles and practice of oncology. Philadelphia: Lippincott; 2005.

[54] Jordan VC. Tamoxifen (ICI46,474) as a targeted therapy to treat and prevent breast cancer. British Journal of Pharmacology. 2006;147(5):S269–S276. Available from: https://doi.org/10.1038/sj.bjp.0706399

[55] Singh S, Gauthier S, Labrie F. Androgen receptor antagonists (antiandrogens) structure-activity relationships. Current Medicinal Chemistry. 2000;7(2):211–247. Available from: https://doi.org/10.1017/j.wsp.0706399

[56] Carter P. Improving the efficacy of antibody-based cancer therapies. Nature Reviews Cancer. 2001;1(2):118–129. Available from: https://doi.org/10.1038/35101072

[57] Chen H-Z, Tian Y, Gao Y-H, Song X-C. The GEMS approach to stationary motions in the spherically symmetric spacetimes. Journal of High Energy Physics. 2004;2004(10):011–011. Available from: https://doi.org/10.1088/1126-6708/2004/10/011

[58] Seyfizadeh N, Seyfizadeh N, Hasenkamp J, Huerta-Yepez S. A molecular perspective on rituximab: a monoclonal antibody for B cell non Hodgkin lymphoma and other affections. Critical Reviews in Oncology/Hematology. 2016;97:275–290. Available from: https://doi.org/10.1016/j.critrevonc.2015.09.001

[59] Albanell J, Codony J, Royvira A, Mellado B, Gascón P. Mechanism of Action of anti-Her2 monoclonal antibodies: scientific update on trastuzumab and 2c4. New Trends in Cancer for the 21stCentury. 2003;253–68. Available from: https://doi.org/10.1016/j.critrevonc.2015.09.001

[60] Jänne PA, Gray N, Settleman J. Factors underlying sensitivity of cancers to small-molecule kinase inhibitors. Nature Reviews Drug Discovery. 2009;8(9):709–723. Available from: https://doi.org/10.1038/nrd2871

[61] Gross S, Rahal R, Stransky N, Lengauer C, Hoeflch KP. Targeting cancer with kinase inhibitors. Journal of Clinical Investigation. 2015;125(5):1780–1789. Available from: https://doi.org/10.1172/JCI76094
[62] Yaish P, Gazit A, Gilov C, Levitzki A. Blocking of EGF-dependent cell proliferation by EGF receptor kinase inhibitors. Science. 1988;242(4880):933–935. Available from: https://doi.org/10.1126/science.3263702

[63] Rivera-Torres J, San José E. Src tyrosine kinase inhibitors: new perspectives on their immune, antiviral, and senotherapeutic potential. Frontiers in Pharmacology. 2019;10. Available from: https://doi.org/10.3389/fphar.2019.01011

[64] Broome JD. L-asparaginase: discovery and development as a tumor-inhibitory agent. Cancer Treat Rep. 1981;65(Suppl 4):111-114.

[65] Gambacorti-Passerini C, Antolini L, Broome JD. Mitotane for adrenocortical carcinoma treatment. Curr Opin Investig Drugs. 2005;6(4):386-394.

[66] Harris PE, Bouloux P-MG. Endocrinology in Clinical Practice. CRC Press; 2014. Available from: https://doi.org/10.1007/b16712

[67] Hahner S, Fassnacht M. Mitotane for adrenocortical carcinoma treatment. Curr Opin Investig Drugs. 2005;6(4):386-394.

[68] Linot B, Campone M, Fassnacht M. Liposomal doxorubicin–cyclophosphamide combination in breast cancer patients with brain metastases: a monocentric retrospective study. Journal of Neuro-Oncology. 2014;117(2):253–259. Available from: https://doi.org/10.1007/s11060-014-1378-5

[69] Bonfante V, Santoro A, Viviani S, Valagussa P, Bonadonna G. ABVD in the treatment of Hodgkin’s disease. Semin Oncol. 1992;19(2 Suppl 5):38-44.

[70] Linot B, Campone M, Augereau P, Delva R, Abadie-Bonfante V, Santoro A, Viviani S, Valagussa P, Bonadonna G. ABVD in the treatment of Hodgkin’s disease. Semin Oncol. 1992;19(2 Suppl 5):38-44.

[71] Diehl V, Behringer K. Could BEACOPP be the new standard for the treatment of advanced Hodgkin’s lymphoma? Cancer Investigation. 2006;24(4):461–465. Available from: https://doi.org/10.1080/07357900600705789

[72] Ali N, Adil SN, Shaikh MU. Autologous Hematopoietic stem cell transplantation – 10 years of data from a developing country. Stem Cells Translational Medicine. 2015;4(8):873–877. Available from: https://doi.org/10.5966/scm.2015-0015

[73] Mori Y, Shima H, Ibara H, Yabumoto H, Iwasaki A, Yoshioka M, et al. BEP (bleomycin, etoposide, cisplatin) therapy for testicular tumors. Hinyokika Kiyo. 1992;38(10):1139-1142.

[74] Rajkumar SV. Multiple myeloma: 2013 update on diagnosis, risk-stratification, and management. American Journal of Hematology. 2013;88(3):225–235. Available from: https://doi.org/10.1002/ajh.23390

[75] Cooper K, Picot J, Bryant J, Clegg A. Comparative cost-effectiveness models for the treatment of multiple myeloma. International Journal of Technology Assessment in Health Care. 2014;30(1):90–97. Available from: https://doi.org/10.1017/S0266462313000615

[76] Offidani M, Corvatta L, Moré S, Nappi D, Martinelli G, Olivieri A, et al. Daratumumab for the management of newly diagnosed and relapsed/refractory multiple myeloma: current and emerging treatments. Frontiers in Oncology. 2021;10. Available from: https://doi.org/10.3389/fonc.2020.624661

[77] Cassidy J, Tabernero J, Twelves C, Brunet R, Butts C, Conroy T, et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. Journal of Clinical Oncology. 2004;22(11):2084–91. Available from: https://doi.org/10.1200/JCO.2004.11.069

[78] Comis RL. Clinical trials of cyclophosphamide, etoposide, and vincristine in the treatment of small-cell lung cancer. Semin Oncol. 1986;13(3 Suppl 3):40-44.

[79] Hayes DF, Henderson IC, Shapiro CL. Treatment of metastatic breast cancer: present and future prospects. Semin Oncol. 1995;22(2 Suppl 5):5-19.

[80] Thakar K, Novero A, Das A, Lisinschi A, Mehta B, Ahmed T, et al. CEPP regimen (cyclophosphamide, etoposide, procarbazine and prednisone) as initial treatment for Hodgkin lymphoma patients presenting with severe abnormal liver function. Biomarker Research. 2014;2(1). Available from: https://doi.org/10.1186/2050-7771-2-12

[81] Yasuda H, Yasuda M, Komatsu N. Chemotherapy for non-Hodgkin lymphoma in the hemodialysis patient: a comprehensive review. Cancer Science. 2021;112(7):2607–2624. Available from: https://doi.org/10.1111/cas.14933

[82] Shaikh H, Umar S, Sial M, Christou A, Kulka-ri A. A case of secondary sclerosing cholangitis in the setting of non-Hodgkin’s lymphoma. Cureus. 2019;11(5):e4707. Available from: https://doi.org/10.7759/cureus.4707

[83] Sitzia J, Huggins L. Side effects of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy for breast cancer. Cancer Practice. 1998;6(1):13–21. Available from: https://doi.org/10.1046/j.1523-5394.1998.1998006013.x
Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastric adenocarcinoma. New England Journal of Medicine. 2006;355(1):11–20. Available from: https://doi.org/10.1056/NEJMoa055531

Petrioli R, Francini E, Roviello F, Marrelli D, Fiaschi AI, Laera L, et al. Sequential treatment with epirubicin, oxaliplatin and 5FU (EOF) followed by docetaxel, oxaliplatin and 5FU (DOF) in patients with advanced gastric or gastrointestinal cancer: a single-institution experience. Cancer Chemotherapy and Pharmacology. 2015;75(5):941–7. Available from: https://doi.org/10.1007/s00280-015-2715-x

Zhang J, Dong R, Shen L. Evaluation and refection on claudin 18.2 targeting therapy in advanced gastric cancer. Chinese Journal of Cancer Research. 2020;32(2):263–270. Available from: https://doi.org/10.21147/j.issn.1000-9604.2020.02.13

Wilson WH, Grossbard ML, Pittaluga S, Cole D, Pearson D, Drbohlav N, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood. 2002;99(8):2685–2693. Available from: https://doi.org/10.1182/blood.V99.8.2685

Öztürk MA, Barştă İ, Altındağ MK, Türker A, Yalcın Ş, Çelik İ, et al. Modified ESHAP as salvage chemotherapy for recurrent or refractory non-Hodgkin’s lymphoma: results of a single-center study of 32 patients. Chemotherapy. 2002;48(5):252–8. Available from: https://doi.org/10.1159/000066768

Fujimura T, Yoshino K, Kato H, Fujisawa Y, Nakamura Y, Yamamoto Y, et al. Case series of BRAF-mutated advanced melanoma treated with encorafenib plus binimetinib combination therapy. The Journal of Dermatology. 2020;48(3):397–400. Available from: https://doi.org/10.1111/1346-8138.15688

Catanecci DVT, Tebbutt NC, Davidenko I, Murad AM, Al-Batran S-E, Ilson DH, et al. Rilotumumab plus epirubicin, cisplatin, and capecitabine as first-line therapy in advanced MET-positive gastric or gastro-oesophageal junction cancer (RILOMET-1): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology. 2017;18(11):1467–1482. Available from: https://doi.org/10.1016/S1470-2045(17)30566-1

Veneziano G, Wosiek J. A supersymmetric matrix model: III. Hidden SUSY in statistical systems. Journal of High Energy Physics. 2006;2006(11):030–030. Available from: https://doi.org/10.1088/1126-6708/2006/11/030

Wu W, Chen J, Deng H, Jin L, He Z, Rao N, et al. Neoadjuvant everolimus plus letrozole versus fluorouracil, epirubicin and cyclophosphamide for ER-positive, HER2-negative breast cancer: a randomized pilot trial. BMC Cancer. 2021;21(1):862. Available from: https://doi.org/10.1186/s12885-021-08612-y

Al-Batran S-E, Hartmann JT, Hofheinz R, Homann N, Rethwisch V, Probst S, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Annals of Oncology. 2008;19(11):1882–1887. Available from: https://doi.org/10.1093/annonc/mdn403

Seymour JF, Grigg AP, Szer J, Fox RM. Fluoruridine and mitoxantrone: effective and well-tolerated salvage therapy in relapsed indolent lymphoproliferative disorders. Annals of Oncology. 2001;12(10):1455–1460. Available from: https://doi.org/10.1023/A:1012551809100

Thompson PA, Tam CS, O’Brien SM, Wierda WG, Stingo F, Plunkett W, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood. 2016;127(3):303–309. Available from: https://doi.org/10.1182/blood-2015-09-667675

Mazzotta M, Pizzuti L, Krasniqi E, Di Lisa FS, Cappuzzo F, Landi L, et al. Role of chemotherapy in vulvar cancers: time to rethink standard of care? Cancers. 2021;13(16):4061. Available from: https://doi.org/10.3390/cancers13164061

Yu K-D, Ye F-G, He M, Fan L, Ma D, Mo M, et al. Effect of adjuvant paclitaxel and carboplatin on survival in women with triple-negative breast cancer. JAMA Oncology. 2020;6(9):1390. Available from: https://doi.org/10.1001/jamaoncol.2020.2965

Seo M-D, Lee K-W, Lim JH, Yi HG, Kim D-Y, Oh D-Y, et al. Irinotecan combined with 5-fluorouracil and leucovorin as second-line chemotherapy for metastatic or relapsed gastric cancer. Japanese Journal of Clinical Oncology. 2008;38(9):589–595. Available from: https://doi.org/10.1093/jjco/hyn078

Gustavsson B, Carlsson G, Machover D, Petrelli N, Roth A, Schmoll H-J, et al. A review of the evolution of systemic chemotherapy in the management of colorectal cancer. Clinical Colorectal Cancer. 2015;14(1):1–10. Available from: https://doi.org/10.1016/j.clcc.2014.11.002
[139] Biersack B. Relations between approved platinum drugs and non-coding RNAs in mesothelioma. Non-coding RNA Research. 2018;3(4):161–173. Available from: https://doi.org/10.1016/j.nerna.2018.08.001

[140] Zinner RG, Fossella FV, Herbst RS. Pemetrexed in advanced NSCLC: a review of the clinical data. Oncology (Williston Park). 2004;18(8 Suppl 5):54–62.

[141] Siegel DS, Schiller GJ, Song KW, Agajanian R, Zinner RG, Fossella FV, Herbst RS. Pemetrexed in patients with cardiac comorbidity: a United Kingdom National Cancer Research Institute Trial. Journal of Clinical Oncology. 2014;32(4):282–287. Available from: https://doi.org/10.1200/JCO.2013.49.7586

[142] Parasramka S, Talari G, Rosenfeld M, Guo J, Villano JL. Procarbazine, lomustine and vincristine for recurrent high-grade glioma. Cochrane Database of Systematic Reviews. 2017(7):CD011773. Available from: https://doi.org/10.1002/14651858.CD011773.pub2

[143] Cummin T, Johnson P. Lymphoma: turning biology into cures. Clinical Medicine. 2016;16(Suppl 6):s125–s129. Available from: https://doi.org/10.7861/clinmedicine.16-6-s125

[144] Carbone J, Perez-Fernandez R, Muñoz A, Sabin P, Carreño L, Fernandez-Cruz E. Combined therapy with rituximab plus cyclophosphamide/vincristine/prednisone for Sjögren’s syndrome-associated B-cell non-Hodgkin’s lymphoma. Clinical Reviews in Allergy & Immunology. 2007;34(1):80–84. Available from: https://doi.org/10.1007/s12016-007-8025-2

[145] Lisenko K, McClanahan F, Schöning T, Schwarzbich MA, Cremer M, Dittrich T, et al. Minimal renal toxicity after rituximab DHAP with a modified cisplatin application scheme in patients with relapsed or refractory diffuse large B-cell lymphoma. BMC Cancer. 2016;16(1):267. Available from: https://doi.org/10.1186/s12885-016-2289-y

[146] Martin A, Conde E, Arnan M, Canales MA, Deben G, Sancho JM, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica. 2008;93(12):1829–1836. Available from: https://doi.org/10.3324/haematol.13440

[147] Fields PA, Townsend W, Webb A, Counsell N, Pocock C, Smith P, et al. De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients with cardiac comorbidity: a United Kingdom National Cancer Research Institute Trial. Journal of Clinical Oncology. 2014;32(4):282–287. Available from: https://doi.org/10.1200/JCO.2013.49.7586

[148] Shea TC, Beaven AW, Moore DT, Serody JS, Gabriel DA, Chao N, et al. Sequential high-dose ifosfamide, carboplatin and etoposide with rituximab for relapsed Hodgkin and large B-cell non-Hodgkin lymphoma: increased toxicity without improvement in progression-free survival. Leukemia & Lymphoma. 2009;50(5):741–748. Available from: https://doi.org/10.1080/10428190902853136

[149] JeonYW, LimST, GwakH, ParkSY,SuhYJ. Clinical Impact of primary prophylactic pegfilgrastim in breast cancer patients receiving adjuvant docetaxel-doxorubicin-cyclophosphamide chemotherapy. Journal of Breast Cancer. 2020;23(5):521-532. Available from: https://doi.org/10.4048/jbc.2020.23.e52

[150] Nakatsuka K, Koyama H, Oouchi Y, Imanishi S, Mizuta N, Sakaguchi K, et al. Docetaxel and cyclophosphamide as neoadjuvant chemotherapy in HER2-negative primary breast cancer. Breast Cancer. 2016;24(1):63–68. Available from: https://doi.org/10.1007/s12282-016-0666-7

[151] Bergen ES, Binter A, Starzer AM, Heller G, Kiesel B, Tendl-Schulz K, et al. Favourable outcome of patients with breast cancer brain metastases treated with dual HER2 blockade of trastuzumab and pertuzumab. Therapeutic Advances in Medical Oncology. 2021;13:175883592110090. Available from: https://doi.org/10.1177/17588359211009002

[152] Juergens C, Weston C, Lewis I, Whelan J, Paulussen M, Oberlin O, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pediatric Blood & Cancer. 2006;47(1):22–29. Available from: https://doi.org/10.1002/pbc.20820

[153] Loehrer PJ Sr, Williams SD, Einhorn LH. Ifosfamide in testicular cancer: the Indiana University experience. Semin Oncol. 1989;16(1 Suppl 3):96-101.

[154] Jaffe N, Paed D, Traggis D, Salian S, Cassady JR. Improved outlook for Ewing’s sarcoma with combination chemotherapy (vincristine, actinomycin D and cyclophosphamide) and radiation therapy. Cancer. 1976;38(5):1925–1930. Available from: https://doi.org/10.1002/jb.202080380510;3.0.CO;2-J
Whelan J, Le Deley M-C, Dirksen U, Le Teuff G, Brennan B, Gaspar N, et al. High-dose chemotherapy and blood autologous stem-cell rescue compared with standard chemotherapy in localized high-risk Ewing sarcoma: results of Euro-E.W.I.N.G.99 and Ewing-2008. Journal of Clinical Oncology. 2018;36(31):3110–9. Available from: https://doi.org/10.1200/JCO.2018.78.2516

Hussein M. Pegylated liposomal doxorubicin, vincristine, and reduced-dose dexamethasone as first-line therapy for multiple myeloma. Clinical Lymphoma. 2003;4:S18–S22. Available from: https://doi.org/10.3816/CLM.2003.s.004

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