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A Comprehensive Review on the Application of Cornerstone Combination Therapy for the Cancer Treatment

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Abstract

The current review focuses on cancer, the second most important disease across the globe. Cancer is a non-communicable disease leading to an alteration in the body at the genetic level. Nearly 130 types of cancers were reported across the world. The classification, diagnostic and treatment methods currently being reported were discussed. It was understood that surgery is the most commonly used therapy for benign tumors or the initial stage tumors. Of the conventional monotherapies, chemotherapy has gained importance to cure or suppress cancer in an economical manner. Besides cure, many side effects, tumor sensitivity, were observed which can range from mild to life-threatening in some patients. Hence, combination therapy combinations of conventional monotherapy came into existence to overcome the side effects economically within less time. In combination therapy, the toxicity of the drugs being used can be minimized as they target the alternate pathway. Of various combinations, targeting the enzymes responsible for tumor growth and metastasis by small molecule inhibitors has gained importance because of high specificity (under clinical studies). Hence, combination therapy is a cornerstone therapy which needs to be evaluated thoroughly among large numbers of people across the world.

Keywords: Cancer, conventional monotherapy, combination therapy, enzymes, side effects, tumor sensitization**,** toxicity, cornerstone therapy.

Introduction to Cancer

Cancer is a non-communicable, multistep, multifactorial, and microevolutionary transformation leading to the replicative immortality of altered cells within the body. Cancer is a directional multifactorial cellular disorder that causes changes at the gene level leading to its malignancy. Worldwide, cancer has gained as the second most important disease based on the number of deaths every year next to heart related disorders (1). The first person to identify and name cancer is Hippocrates (2). More than 100 kinds of malignancies have been reported by analysts, out of which 22% are because of tobacco, 10% were because of food habits and obesity, viral infections constitute 15% and hereditary constitutes 5-10%.

Global Statistics on Cancer

Based on the WHO statistics, it was understood that the incidence rate of mortality is approximately 8 million in a year. Researchers in 2007 have reported the mortality rate as 45 percent which increases to 65 percent by 2030 (3). Based on the GLOBOCAN cancer statistics 2018 the estimated number of cancer cases is approximately 18.1 million and the

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the mortality rate was approximately 9.6 million (4). Based on the total number of deaths lung cancer stands first with the incidence mortality of 18.4%. The incidence mortality rate of breast, prostate, colorectal, stomach, and liver cancers were 11.6 %, 7.1%, 6.1%, 9.2 %, 8.2%, and 8.2% respectively. The most commonly seen cancers among males are lung, followed by other cancers, (prostate and gastrointestinal cancers). Besides, in females the most diagnosed cancer is breast cancer followed by others. Lifestyle and geographical distribution are some of the most important factors associated with cancer (5). In 2012, approximately 14.1 million cases were reported across the world, out of which the incidence rate of mortality rate is 8.2 million (6). It was understood that the number of deaths reported from middle and low-income countries was relatively high in comparison with high-income countries. Of the new cancer cases reported across the word 57% constituted from low-income countries and the number of deaths was approximately 67% of the reported cases. Early detection and treatment results will improve the survival rates, reduce the healthcare burden and improves the overall economy.

Each year increased survival rate results in saving 2.4-3.7 million lives (7). The factors contributing for the cancer progression are genetic disorders, radiation, obesity, stress, smoking, geographical, race, and occupation (2, 8). It was also reported that diabetes was one of the main causes of cancer. Some of the reasons are the limited expression of tumor suppressor genes and alteration of both metabolic and signaling pathways leading to the production of various angiogenic factors as well as nutrients required for their progression (9). It was also reported that radiation therapy is the first diagnostic method used to diagnose cancer. The other treatments currently available in the market are phototherapy, combination therapy, immunotherapy, chemotherapy, enzymatic therapy, radical therapy, adjuvant therapy, and many others (10-14).

Some of the commercially available drugs to treat cancer or reduce the cell division of cancer cells are Vincristine, Daunorubicin, Cyclophosphamide, L-Asparaginase, L-Glutaminase etc. with observed side effects (15-18).

Classification of Cancer

Mainly the cancers are classified based on their moment, organ, and tissue origin. These are further sub-classified into different types.

Tumor classification based on their moment

Based on their moment inside the body, fluid tumors are classified into benign (static) and malignant (metastatic).

Benign tumor

The static noncancerous abnormal lumps inside the body are benign tumors. Because of their restricted moment, it is easy to remove them by surgery. The weight of the tumor in some cases will be pounds and large benign tumors sometimes press the surrounding vital organs. Most of the benign tumors do not reoccur after their removal and in rare cases, it was also reported that their reoccurrence can be seen at the same place. Ex: intestinal polyps, uterus fibroids. Benign tumors can be fatal if they grow inside the brain as it is difficult to remove them by surgery. It was also reported that in some cases the benign tumors become malignant. Ex: polyps in the intestine.

Malignant tumor

The cancerous tumors invading from one organ to other organs with the help of body fluids (blood and lymph) are called malignant tumors.

Cancer metastasis

The moment of cancer cells is called metastasis. It was also reported that the 90 % mortality rate of cancer patients depends on the tumor metastasis which can be decreased by the early detection of the tumor (19).

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Detachment, migration, invasion, and adhesion are the four metastatic steps involved in the tumor progression from the primary site to the distal site through blood and lymph flow (19). Metastasis results change in both metabolic as well as signaling pathways resulting in the synthesis of nutrients and growth factors required by the tumor cells for their progression. It was also understood from the literature that the tumor at the distal site is more fatal in comparison with tumors at their primary or origin site. It is also important to understand the origin of the tumor during the diagnosis of the tumor. Many targeted therapies by small molecule inhibitors, radiation therapy, and chemotherapy were currently in use.

Tumor classification based on origin

Based on the primary site of tumor origin, the tumors were defined based on their organ origin. Ex: Breast cancer, lung cancer, renal cancer, brain cancer, and others.

Tumor classification based on tissue type

The international classification of diseases for oncology classified cancers was classified into 6 types based on tissue types. Ex: Sarcomas, Lymphomas, Central Nervous System (CNS) related cancers, and many. Some of the reported cancers are carcinomas (skin cancer), leukemia (blood cancer), sarcomas (connective tissue cancers), lymphomas (immune system) myeloma (progenitor cells), and CNS cancers (brain and spinal cord).

Carcinomas

Cancer of epithelial origin which covers both inner and outer surfaces of the body is called Carcinoma. DNA damage or alterations of genes leads to Carcinoma (20-21). Skin cancer, oral cancers, breast cancer, ovarian cancer, gastrointestinal cancer, liver cancer are some of the reported carcinomas. The most common causative agents are alcohol, virus, tobacco, mutations, and many. Based on their origin again carcinomas were subclassified into a). Adenocarcinoma: glands related cancer associates with mucosa, and b). Squamous cell carcinoma: originates from squamous epithelium. The most common adenocarcinoma across the world is gastrointestinal cancer (GI) and is associated with the gastrointestinal tract. It constitutes about ~ 95% of the reported carcinomas reported worldwide.

Gastrointestinal cancer: GI cancer is multi-step and multi-functional related to both the upper and digestive tract: stomach, esophagus, intestine, liver, pancreas is called gastrointestinal cancer. Many factors contribute to gastrointestinal cancer. It includes biological agents like *Helicobacter pylori*, inflammation, and other physiological factors. The most important factor causing gastrointestinal cancer is oxidative stress. Hence, supplementation with antioxidant foods regulates cancer. The symptoms observed in gastrointestinal cancer are mostly digestion problems, bleeding, weight loss, abdominal pain, vomiting, and others vary from one type of cancer to other. It was understood that Smoking, obesity, food, and drinking lifestyle habits mainly influence the progression of cancer and sometimes are involved in the initiation of the tumor also. In some cases, Geographical distribution also influences the incidence of GI cancer (22). **Diagnostics and Treatment of GI cancer:** The diagnostic methods used for the detection of gastrointestinal cancers are endoscopy and biopsy. The treatment of each cancer varies from person to person depending on the origin and location of the tumor. Chemotherapy is the most commonly used method to cure gastrointestinal cancers. Radiation and surgery were the other methods used for the diagnosis of GI cancer. A balanced diet enriched with phytochemicals was also reported to prevent cancer.

Leukemia

Cancer-related to blood is called Leukemia. The most commonly affected blood cells are White Blood Cells (WBC). Based on the onset of symptoms, the leukemia was classified

into acute (where the tumor cells multiply quickly) and chronic (the progression of the cancer is very slow). Leukemia was classified into two types as myelogenous leukemia and lymphocytic leukemia based on their progenitor origin (23-25). Based on both progenitor origin and onset of symptoms, the leukemia was classified into 4 types (Figure 01). The most commonly observed symptoms in leukemic patients are sweating, fatigue, weight loss, fever, swollen lymph nodes, bleeding, etc. As leukemia is malignant, it can spread to other organs like the heart, kidneys, and lungs. Many diagnostic tests are developed to identify the type of leukemia and chemotherapy, transplantation, targeted therapy, radiation therapy, and immune therapy was used to treat leukemic patients.

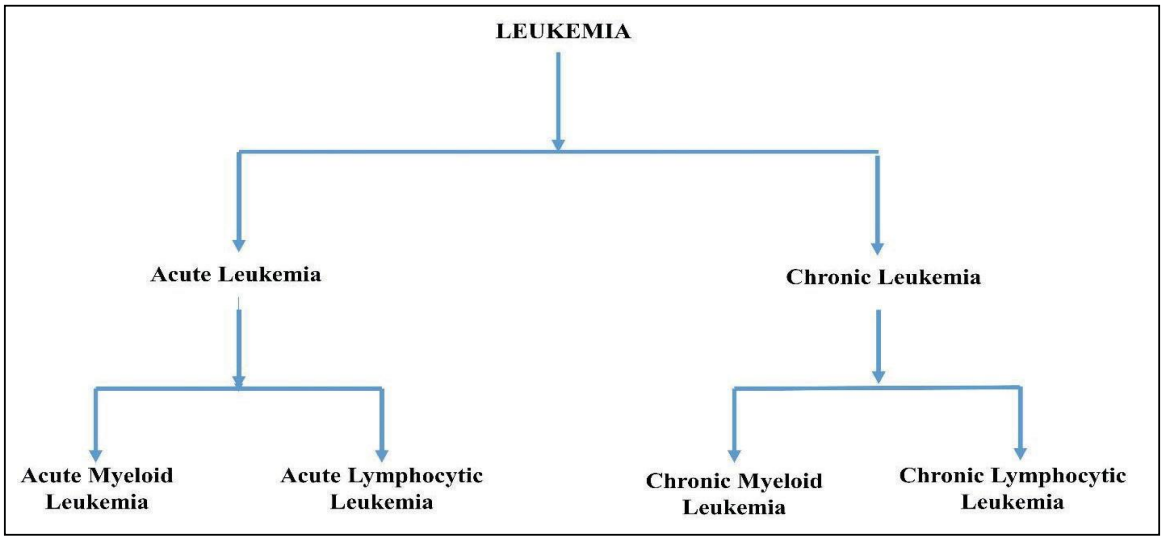

Figure 01. Classification of Leukemia

Sarcoma

Sarcoma is cancer associated with connective tissues like muscles, bones, tendons, and others. Osteosarcoma is the most reported Sarcoma (26,27). Nearly 50 different types of sarcomas are reported. Based on the tissue type sarcoma are classified into soft tissue sarcoma and osteosarcoma. The symptoms observed among sarcoma patients are lumps, bone pain, breathing problems, swelling, etc. Sarcoma causative agents are genetic disorders, radiation, hereditary, and other bone disorders. Biopsy, CT scan, MRI scan, and ultrasound are the diagnostic methods used to treat sarcoma. Surgery, radiation therapy, chemotherapy, targeted therapy. Ex: Osteosarcoma (Bone cancer) (28), angiosarcoma (29) (blood vessels), etc.

Lymphoma

Cancer-associated with the lymphatic system is lymphoma where there is an abnormality in the cell division of lymphocytes leading to their accumulation in lymph nodes which results in the alteration of lymph nodes function. Stomach, breast, spleen, lymph nodes thymus are some organs associated with lymphoma. These are also referred to as solid cancers which were further sub-classified into Hodgkin lymphoma (30) and non-Hodgkin lymphoma (31). The causes of lymphoma were viral infection, weak immune system, radiation, etc. The symptoms observed in lymphoma patients are cough, fever, weight loss, fatigue, etc. Blood tests and imaging tests (CT scan, MRI, X-ray) can be used to diagnose lymphoma. Chemotherapy, radiation therapy,

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Immunotherapy and targeted therapy were used to treat both Hodgkin lymphoma and non-Hodgkin lymphomas.

Myeloma

The cancer associated with the abnormal division of blood plasma cells is Myeloma (32). It starts in the soft tissue of bone marrow. The causes of multiple myeloma are age, heredity, obesity, etc. pain, fatigue, fever, weight loss, anemia, etc. are observed in the advanced stages of myeloma. Smoldering myeloma is the initial stage of myeloma. It affects bones, kidneys, and other organs that are diagnosed by blood, imaging, and urine tests (33). Immunotherapy, chemotherapy, adjuvant therapy, radiation therapy are the most commonly used therapeutic methods to treat myeloma.

Central nervous system associated cancers

The cancers associated with both the brain and spinal cord are CNS cancers (34). The most commonly associated cancer is a glioma. Glioma is associated with the connective tissue called glial cells (35). Both benign (non-cancerous) and malignant cancers were reported as trocytoma, ependymoma (36), germ cell tumor, and other types of CNS cancers. The other types of cancers reported are mixed type (Ex: carcinosarcoma, mesodermal tumor, and others). Radiation, viruses, and head injury are some of the causes of CNS cancers. The symptoms observed are nausea, vomiting, headache, vision problems, etc. MRI, CT scan, biopsy are the diagnostic methods used to detect CNS cancers.

Stages of cancer

Alterations in the genes lead to gain or loss of the gene leading to tumorigenesis. Mutagens (physical and chemical) are the environmental factors leading to the progression of cancer. Some of the cancers are caused by biological agents like human papillomavirus, Epstein–barr virus, etc. Stages are nothing but the extent of cancer within the body. The stages mainly describe the size, organs/tissues affected, and whether the cancer is metastasized. It mainly helps to diagnose cancer. Currently, imaging techniques, biopsy, tissue examinations were used to study cancer in detail. Generally, the appearance of cancer symptoms to its metastasis to other parts of the body is classified into 4 stages. A higher number indicated an advanced stage which sometimes leads to the death of the patient. It was also reported that some cancers start with Stage 0 (less harmful) and the cancers at this stage can be treated by surgery. The process taking place at different stages of cancer was described as follows: Stage 0 - in situ cancer (in place cancer), Stage I-Small tumor developed in a particular organ/tissue, Stage II-Tumor size increased and spread outside the particular organ/tissue, Stage III-Tumor spreads to the surrounding organs, and Stage IV-Metastasis and spreads the tumors across the body. Symptoms of Cancer: The symptoms observed among cancer patients are weight loss, lumps, bleeding, cough, pain fatigue, breathing-related problems, and others (1, 23).

Diagnosis and treatment of tumor

Tumor Diagnosis: To treat cancer, it is important to know the type, size, and stage of cancer. Both imaging and lab tests are in use for the detection of tumor (37).

Complete blood count (Leukemia), blood chemistry profile, and cytogenetic analysis (base on the white blood cell count) are the blood tests used for the detection of cancers.

Urinalysis helps in the detection of kidney and uterus related cancers.

Biopsy- where surgically removed tissue is sent for examination and various types of biopsy are performed based on the tumor location and tumor type. Fine needle aspiration (FNA), core biopsy, Excisional biopsy, Incisional biopsy, Endoscopic biopsy, Laparoscopic biopsy, and skin biopsy are the different types of biopsy in use.

Cytology tests are used for the examination of

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body fluids like cerebrospinal fluid (brain cancer), pleural fluid (lung cancer), and others. The variants of cytology tests are scrape cytology and Pap smear tests.

X-rays, CT scan, ultrasound, MRI scan, Mammography, Endoscopy, and others are the imaging tests used for the detection of tumors (38-39).

Screening tests differ from one type of cancer detection to other types. Ex: Sigmoidoscopy (colorectal cancer), HPV test (cervical cancer), PSA test (prostate cancer) (40- 42).

Treatments of cancer surgery

Surgery is one of the most commonly used treatments to cure cancer with exceptional cancers associated with leukemia. Surgery is more effective to treat the cancer at initial stages and it can be used in combination with chemotherapy and other treatments for the reduction of size tumors (ex: brain tumors) (43-45). Surgery can be used to cure, debulk, and palate cancer. The side effects associated with surgery are bleeding, anesthesia complications, and infections. Many advanced surgeries like lumpectomy, radical mastectomy, video-assisted thoracoscopic surgery (lung cancer treatment) are being used to remove the tumor within less time besides unaffecting/minimal effect on the surrounding tissues or organs (46). Robotic surgery, Laser surgery, electrosurgery, and cryosurgery are the special variants of surgery being used to treat cancer (43, 47-49).

Radiation therapy

In Radiation therapy the tumor cells were destroyed by the use of high energy X-rays (50). Radiation therapy can be given externally or internally. The internal radiation therapy is known as brachytherapy by the implantation of radioactive material. Some of the tumors which cannot be removed by the surgery are removed by radiation therapy (51). Radiation therapy can be used in combination before the surgery for the reduction in tumor size as neoadjuvant therapy (ex. Lung cancer) and after surgery as adjuvant therapy (ex. Mastectomy). To relieve pain, palliative radiation therapy is used. External beam radiation therapy, Intensity-Modulated Radiation Therapy (IMRT), brachytherapy, proton therapy, systemic radiation therapy, and gamma knife were the different ways of radiation therapy (52-54). The side effects observed in the patients treated with radiation therapy are redness, fatigue, pneumonia, etc.

Immunotherapy

Immune system boosting with the help of inbuilt or synthetic compounds (synthesized in the laboratory) to defend against the cancer cells is known as Immunotherapy. Immunotherapy destroys the tumor or it is being used to suppress the growth of the tumor cell. Monoclonal antibodies (a kind of targeted therapy), T-cell therapy, oncolytic virus therapy, checkpoint inhibitors, etc. are some of the Immunotherapies in use (12, 55-59). FDA in 2015 approved the Oncolytic virus - the genetically modified virus having an anti-tumor vaccine to treat advanced melanoma tumor cells. The virus used was the T-VEC (talimogene laherparepvec) (60). Usage of interleukins and interferons comes under non-specific immunotherapy which can be used in combination with chemotherapy or radiation therapy (61). Allergies and inflammation are the most commonly seen symptoms and the patients treated with Immunotherapy.

Hormonal therapy

Hormonal therapy is also known as endocrine therapy used to treat sensitive cancers, recurrence minimization, and others (62). Increased production of the hormones results in the development of cancers like breast cancer, ovarian cancer, prostate cancer, etc. (63). Endocrine therapy aids in tumor suppression by blocking the stimulating effects of the cancers or by the hormones produced. Tamoxifen is one such compound being used to treat breast cancer (20, 64). The route of hormonal inhibitors was via oral or intravenous or surgery (removal of hormone-producing organs). In

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some cases, the removal of the organs by surgery prevents cancers. (Ex: oophorectomy) with some side effects like dryness etc. It can be given in combination with other therapies to reduce the size of the tumor (neoadjuvant therapy) or as adjuvant therapy or to kill the metastasis or recurred tumor. Some of the commercially available hormonal drugs are Abiraterone, Exemestane, Leuprolide etc. against prostate, breast, and uterine cancer (65,66).

Chemotherapy

The application of chemically synthesized small molecule inhibitors against cancer cells is known as chemotherapy (13). In chemotherapy, the drugs inhibit the signaling pathways triggering the tumor cell multiplication besides induces apoptotic signal which leads to the death of cancer cells. Vincristine, Daunorubicin, Cyclophosphamide, etc. are the commercially available drugs to treat different cancers with some observed side effects like fever, hair loss, weight loss, inflammation, allergies, hypersensitivity reactions, inflammation, and others (67). In most of the cases, the side effects are short term with exceptional long-term effects associated with heart problems. The chemotherapeutic mainly targets the cell multiplication of the tumor cells. Chemotherapy is more effective against rapidly multiplying tumors besides indolent tumors. Neoadjuvant, adjuvant and palliative chemotherapy are the variants of chemotherapy. The route of administration is via intravenous, oral or directly into the fluids surrounding the organs. The diagnosis depends on the stage of cancer and the financial status of the patient. Various side effects are observed in the chemotherapy treatment (13). Some are immediate effects (hair loss, skin, and gastric problems) and some effects are observed late and these effects depend on the dose and toxicity of drugs administered during treatment. Based on their toxicity the side effects were classified into four groups as Mild symptoms-grade 1, moderate symptoms-grade 2, severe symptoms-grade 3 and life threatened symptoms as grade 4 (Neurotoxicity, paralysis, comma, etc.) psychological problems, nausea, vomiting, gastrointestinal disorder, drug resistance, infertility, carcinogenicity, fatigue, sleep disorder, mucositis (68,69). The application of phytochemicals (phenols and others) can minimize drug resistance. Targeted therapy has gained importance which uses small molecule inhibitors, monoclonal antibodies, enzymes, cytostatic drugs, and oncolytic virus to treat cancer prognosis (13,58,70). The efficacy of cytostatic drugs depends on tumor response, survival time, and toxicity. Chemotherapy is effective against lymphomas and carcinomas (71).

Enzymatic therapy

Application of enzymes as drug to treat diseases has gained importance because of its economic feasibility and high specificity towards its substrate (72, 73). It will uphold various physiological conditions and eliminate it from the body in a reasonable time. Currently, enzymes are being used to treat gastrointestinal disorders, Gaucher's disease, liver failure, gout, coronary heart disease, cancer, etc. Many enzymes like L-Asparaginase and L-Glutaminase are being studied because of their ability to treat cancer with minimal side effects as these compounds convert the metabolites required by the tumor supplement for the production of energy. The enzymes supplied by the external route of administration will convert metabolites into unusable form leading to the death of tumor cells due to lack of energy supplements. Mulluer et.al worked on the application of Folylpolyglutamate synthetase validation by UPLC-MS/MS-based method (quantifies L-Glutamic acid) on the leukemic cell lines as well as clinical samples (74). In addition, the enzymes were also used in suicide gene therapy (Enzyme prodrug therapy) in which converts the prodrug administered into tumor toxic form leading to the death of tumor cells (16). It was also reported that modified enzymes have high stability with observed fewer side effects against cancer patients. Hence, this therapy can be given individually or in combination with

other chemotherapeutic drugs that may have lesser side effects.

Combination therapy

The most common problem associated with many therapies is drug resistance and sensitization of the tumor cells which can be prevented by the application of combination therapy (75,76). The approval time for a drug to enter into the market takes approximately 15 years. Unlike conventional methods that are not specific towards tumor cells, combination therapy-specific towards its targets. The non-specific nature of conventional methods leads to many side effects. The treatments available in the market are not economically feasible and consume a lot of time having side effects. Hence, a combination of therapeutic approaches can be used to overcome the drawbacks of the monotherapy (56). The cornerstone therapy which has gained importance in recent days is combination therapy. In combination therapy, various treatments used to treat cancer are combined to minimize or remove the cancer tumors in an effective way. Combination therapy is an effective measure against drug resistance which induces the apoptotic signal/or hinders the tumor growth (59, 77, 78). Even in combination therapy side effects are observed but with less toxicity as various pathways are targeted. The first proven concept of combination therapy against leukemic cancer was postulated by Emil Frei, James F. Holland, and Emil J. Freireich in 1965 (79).

Combination therapy is a synergic approach that involves a combination of anti-cancer drugs to specifically target the cancer cells with minimal side effects. The drawbacks of monotherapy are drug resistance as the cancer cells chose alternate pathways for multiplication, sensitization and other drawbacks in monotherapy is the drug targets both tumor and normal cells and these can be prevented by the application of combination therapy which uses cell cycle regulators and apoptotic inducers cost-effectively (80). The usage of antagonist drugs in combination therapy prevents the cytotoxicity of normal cells (81-83). The emerging variant of combination therapy is restrictive combination targeting the tumors based on the presence or absence of specific markers on both normal and tumor cells.

Drug repositioning is the use of the commercially available drugs which are being used to treat various diseases to diagnose cancer. Hence the application of the repurposed drug in combination with cytotoxic drugs will be effective in diagnosing tumors. Carbonic anhydrase which is used to treat glaucoma and sickness has anti-cancer potential (84). Raplog is another drug that is being used in graft rejection as an immunosuppressant as it has anti-cancer properties (12). Histone deacetylase inhibitors in combination with Trichostatin A an antifungal antibiotic to treat cancer is under clinical trials (85,86). The first FDA approved repurposed drug is Vorinostat used to treat cutaneous T-cell lymphoma. Romidepsin and panobinostat are the other drugs that have the efficacy to treat cutaneous T-cell lymphoma and multiple myeloma respectively (57,87-89). The combination of romidepsin and gemcitabine (Phase I) is being used to treat solid tumors of the pancreas, lung, breast, and ovaries with observed side effects like nausea, vomiting, and hematological abnormalities (90). The combination of itraconazole and penetrexeol is under clinical trials to treat lung cancer and pancreatic cancer (91-93). This combination inhibited the endothelial cell proliferation of cell lines both in-vitro and in vivo. The anti-cancer effect against HT29 colon cancer cell lines by using Bevacizumab and curcumin combination was demonstrated by Yue et.al. (94) Kato et.al used gefitinib and erlotinib combination to treat lung cancer (95). Amado et.al in 2008 used panitumumab in combination with cetuximab to treat colon cancer (96,55). It was reported by Quinn et.al that the application of combination therapy to prevent ductal adenocarcinoma. They demonstrated that the drugs target the selective apoptotic pathway leading to the death of tumor cells. The combination of pan-Bcl-2 inhibitor and minocycline was used for the diagnosis of pancreatic cancer (97). The combined effects of the drugs were proved

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both in-vitro and in vivo.

Oncolytic therapy is the use of an oncolytic virus to target the tumor cells besides leaving normal cells. It was understood that conventional therapies are less effective for metastatic cancer. The combination therapy of oncolytic virus with conventional therapies is under clinical trials (58). Re-engineering of the virus at the gene level to specifically target the tumor cells is being carried out in adenovirus, herpes- viruses, etc. dl1520, CV890, CV706 administration either by intratumoral, intraperitoneal, or intravenous in combination with 5-fluorouracil treat head and neck squamous cell carcinoma, gastric carcinoma is under clinical trials stage II. It was also reported that many wild type viruses have anti-tumor properties. The wild type viruses having cytotoxic properties are vaccinia virus, Newcastle disease virus, parvovirus, etc. The most common side effects observed with oncolytic therapy are flu-like symptoms. The combination of oncolytic viruses and radiation therapy is at the preclinical stage. These experiments were reported on human glioma xenograft models with or without p53 mutant by dl1520 injections followed by radiation (58). Ivana Bozic in 2013 worked on the effect of combination therapy myeloma patients to overcome drug resistance. They developed a mathematical model to analyze the number of lesion w.r.t. treatment. They have given combination therapy to 20 myeloma patients administered with vemurafenib and observed that the results are effective for the long term unless any mutation is observed. In the case of mutation observance, triple therapy is suggested (82). The developed mathematical model was also used to study the combined effects against pancreatic and colorectal metastatic cancers.

Feldmann et.al worked on the application of combined therapy by using the inhibitors that block the hedgehog signaling pathway for the diagnosis of pancreatic cancer. They reported that there is a significant decrease in the tumor size and metastasis phenomena in mice when a combination of Gemcitabine and Cyclopamine is administered (98). Hence, hedgehog signaling inhibitors may be a new emerging solution for pancreatic cancer treatment (99). Frew et.al worked on the combination therapy of histone deacetylase inhibitors and mouse-specific monoclonal antibodies MD5-1 against mouse breast cancer models. They reported that these both have been used as monotherapy to treat various tumors which are under clinical trials (86). Hence, the combination of Vorinostat with MD5-1 induces anti-tumor properties in mouse breast cancer models as the combination induces activation of both intrinsic and extrinsic apoptotic pathways both in-vitro and in vivo (21, 75, 100, 101). Various combinations of drugs are under clinical trials showing promising results. Some of the combinations of drugs that are being studied were shown below Table 01.

It was reported by many researchers that targeting the metabolic / signaling pathway enzymes which are involved in tumor progression can be effective in tumor suppression with minimal side effects. Elisa Bergaggio worked on the inhibitors that target the mutated isocitrate dehydrogenases which lead to cancers (14). These enzymes can be used as markers for the detection of cancers. Hence, potential targets need to be studied against these mutated enzymes (14). Another researcher William j. Israelsen et.al worked on pyruvate kinase regulators to treat cancer (108). The pyruvate kinases are involved in glycolysis and are understood to be 4 types having unique properties. Of which pyruvate kinase isoform 2 is involved in both cell cycle progression (108). Hence, pyruvate kinase inhibitors may be an emerging idea for tumor treatment. Khushwant et.al reviewed the application of small molecule kinase inhibitors which are involved in tumor suppression (109). They have reported that nearly 37 kinase inhibitors were approved by the FDA to treat breast and lung cancer patients, while many others are in clinical phase studies (109).

Biagio Ricciuti worked on enzymatic inhibitors that control angiogenesis as promising emerging targets (9,110). Small molecules targeting nitric oxidase and metalloproteinase

Table 01. Various Combinations of drugs under Clinical trial studies

COMBINATIONS	ANTI-TUMOR PROPERTIES	REFERENCE
VEGFR antibody DC101+Vinblastine	Tumor regression in neuroblastoma xenograft models	102
Bevacizumab+Paclitaxel	Metastatic breast cancer	103
Sorafenib+ Dacarbazine/Capercit-abine	Breast cancer (phase 2 trials)	78
Cetuximab +Gemcitabine	Pancreatic cancer (phase 2)	104
Erlotinib+Gemcitabine	Pancreatic cancer (phase 3)	105
Bevcizumab + Everolimus	Melanoma and colorectal cancer	106
Imatinib + Peginterferon	Gastrointestinal stromal tumor patients	107
Vorinostat + MD5-1	Brest cancer mouse models	86
Gecitabine + Cyclopamine	Pancreatic cancer	98, 99
ncolytic virus dl1520+ 5-fluorouracil	Head and next squamous cell carcinoma, gastric carcinoma (Phase 2)	58
pan-Bcl-2 inhibitor + Minocycline	Pancreatic cancer	97
Gefitinib + Erlotinib	Lung cancer	95
Panitumumab + Cetuximab	Colon cancer	96
Bevacizumab + Curcumin	HT29 colon cancer cell lines	94
Itraconazole + Penetrexeol	Lung cancer	92
Histone deacetylase inhibitors +Trichostatin A	Various Cancer	86
Romidepsin+ Gemcitabine	Solid tumors	90

are not effective in clinical studies. Besides, heparanase, NADH oxidase, lysyl oxidase small molecule inhibitors showed promising results studying these enzyme inhibitors can be effective. Iqra Sarfraz worked on the malic enzyme 2 inhibitors as this enzyme is over expressed and is seen in various cancers-hepatomas, lung cancer, melanomas, osteosarcomas, etc. (111).

Wen et.al reported NPD389 inhibitors against malic enzymes which need to be further evaluated (112). Embonic acid is a competitive small molecule inhibitor of malic enzyme which induces senescence on H1299 cell lines and the effects of embonic acid on other cell lines needs to be evaluated further (112,113). Similarly targeting phosphoglycerate mutase-1 by small molecule inhibitors can be further evaluated with combination therapy (114).

Summary of the review

It was understood from the literature that based on the statistics, cancer is the second most important disease which needs attention for the cure. A diverse range of cancers was identified across the world which is influenced by geographical distribution, food habitats, pollution, and other environments and mutagens (both physical and chemical). Various treatments are currently in use with many side effects, some of them are life-threatening. In addition to the present treatment, and many clinical trials are going on the application of combination therapy to treat cancer as well as minimize the side-effects within less time. Various combinations are currently in clinical stud-

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ies of which some of them are effective and some are not and it depends on the tumor properties and combinations of therapy that need to be changed for different types of cancer. Hence, combination therapy will be a promising emerging therapy that needs to be thoroughly evaluated further by targeting the enzymes responsible for tumor prognosis. Hence, if this therapy succeeds shortly, it will be economical and have minimal side effects as the combination of therapies reduces the toxicity caused by the monotherapy.

References

1. Durthi CP, Pola M, Rajulapati SB, Kola AK, Kamal MA. Versatile and Valuable Utilization of Amidohydrolase L-glutaminase in Pharma and Food industries: A Review. Current Drug Metabolism. 2020;21(1):11-24.

2. Pola M, Durthi CP, Erva RR, Rajulapati SB. Multi Gene Genetic Program Modelling on L-Asparaginase Activity of Bacillus Strato- sphericus. Chemical Product and Process Modeling. 2019.

3. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin D, Piñeros M, Znaor A, Bray F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. International journal of cancer. 2019;144(8):1941-53.

4. Milroy MJ. Cancer statistics: Global and national. Quality Cancer Care: Springer; 2018. p. 29-35.

5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.

6. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. The Lancet Global Health. 2016;4(9):e609-e16.

7. De Souza JA, Hunt B, Asirwa FC, Adebamowo C, Lopes G. Global health equity:cancer care outcome disparities in high-, middle-, and low-income countries. Journal of Clinical Oncology. 2016;34(1):6.

8. Pola M, Rajulapati SB, Durthi CP, Erva RR, Bhatia M. In silico modelling and molecular dynamics simulation studies on L-Asparaginase isolated from bacterial endophyte of Ocimum tenuiflorum. Enzyme and microbial technology. 2018;117:32-40.

9. Ricciuti B, Foglietta J, Chiari R, Sahebkar A, Banach M, Bianconi V, Pirro M. Emerging enzymatic targets controlling angiogenesis in cancer: preclinical evidence and potential clinical applications. Medical Oncology. 2018;35(1):4.

10. Ng CW, Li J, Pu K. Recent Progresses in Phototherapy-Synergized Cancer Immunotherapy. Advanced Functional Materials. 2018;28(46):1804688.

11. Horo H, Porathoor S, Anand R, Kundu LM. A combinatorial approach involving E. coli cytosine deaminase and 5-fluorocytosine-nanoparticles as an enzyme-prodrug therapeutic method for highly substrate selective in situ generation of 5-fluorouracil. Journal of Drug Delivery Science and Technology. 2020:101799.

12. Blagosklonny MV. Immunosuppressants in cancer prevention and therapy. Oncoimmunology. 2013;2(12):e26961.

13. Schirrmacher V. From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment. International journal of oncology. 2019;54(2):407-19.

14. Bergaggio E, Piva R. Wild-type IDH enzymes as actionable targets for cancer therapy. Cancers. 2019;11(4):563.

15. Durthi CP, Pola M, Kola AK, Rajulapati SB. Screening, optimization of culture conditions and scale-up for production of the

L-Glutaminase by novel isolated Bacillus sps. mutant endophyte using response surface methodology. Biocatalysis and Agricultural Biotechnology. 2019;18:101077.

16. Pola M, Durthi CP, Rajulapati SB. Modeling and Optimization of L-Asparaginase production from novel Bacillus stratosphericus by soft computing techniques. Current Trends in Biotechnology and Pharmacy. 2019;13(4):438-47.

17. Durthi CP, Pola M, Podha S, Rajulapati SB. Genetic Algorithm Optimization of L-Glutaminase from novel mutated Bacillus sps. Current Trends in Biotechnology and Pharmacy. 2019;13(1):50-7.

18. Durthi CP, Pola M, Rajulapati SB, Kola AK. Insights into Potent Therapeutical Antileukemic Agent L-Glutaminase Enzyme Under Solid-State Fermentation: A Review. Current Drug Metabolism. 2020.

19. Guan X. Cancer metastases: challenges and opportunities. Acta pharmaceutica sinica B. 2015;5(5):402-18.

20. George A, McLachlan J, Tunariu N, Della Pepa C, Migali C, Gore M, Kaye S, Banerjee S. The role of hormonal therapy in patients with relapsed high-grade ovarian carcinoma: a retrospective series of tamoxifen and letrozole. BMC cancer. 2017;17(1):456.

21. Sastry YN, Bishayee A, Kaladhar D, Kumar AB, Umadevi P, Swathi P, Chandrasai P, Rao DG, editors. Dammarane triterpenoid 1 induces apoptosis in human prostate carcinoma DU145 cells via intrinsic pathway. Anti-Cancer Drugs; 2015: Lippincott Williams & Wilkins Two Commerce Sq, 2001 Market St, Philadelphia.

22. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Przeglad gastroenterologiczny. 2019;14(1):26.

23. Erva RR, Rajulapati SB, Durthi CP, Bhatia M, Pola M. Molecular dynamic simulations of Escherichia coli L-asparaginase to illuminate its role in deamination of asparagine and glutamine residues. 3 Biotech. 2016;6(1):2.

24. Reddy ER, Babu RS, Chandrasai PD, Madhuri P. Neural Network Modeling and Genetic Algorithm Optimization strategy for the production of Lasparaginase from Novel Enterobacter sp. Journal of Pharmaceutical Sciences and Research. 2017;9(2):124.

25. Reddy ER, Babu RS, Chandrasai PD, Madhuri P. Exploration of the binding modes of L-asparaginase complexed with its amino acid substrates by molecular docking, dynamics and simulation. 3 Biotech. 2016;6(1):105.

26. Osasan S, Zhang M, Shen F, Paul PJ, Persad S, Sergi C. Osteogenic sarcoma: a 21st century review. Anticancer research. 2016;36(9):4391-8.

27. Lindsey BA, Markel JE, Kleinerman ES. Osteosarcoma overview. Rheumatology and therapy. 2017;4(1):25-43.

28. Harrison DJ, Geller DS, Gill JD, Lewis VO, Gorlick R. Current and future therapeutic approaches for osteosarcoma. Expert review of anticancer therapy. 2018;18(1):39-50.

29. Shustef E, Kazlouskaya V, Prieto VG, Ivan D, Aung PP. Cutaneous angiosarcoma: a current update. Journal of clinical pathology. 2017;70(11):917-25.

30. Shanbhag S, Ambinder RF. Hodgkin lymphoma: a review and update on recent progress. CA: a cancer journal for clinicians. 2018;68(2):116-32.

31. Armitage JO, Gascoyne RD, Lunning MA,

Vol. 18(4) 2085-2102, October 2024, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2024.4.53

Cavalli F. Non-hodgkin lymphoma. The Lancet. 2017;390(10091):298-310.

32. Naymagon L, Abdul-Hay M. Novel agents in the treatment of multiple myeloma: a review about the future. Journal of hematology & oncology. 2016;9(1):1-20.

33. van Beurden-Tan CH, Franken MG, Blommestein HM, Uyl-de Groot CA, Sonneveld P. Systematic literature review and network meta-analysis of treatment outcomes in relapsed and/or refractory multiple myeloma. Journal of Clinical Oncology. 2017;35(12):1312-9.

34. Lucas C-HG, Solomon DA, Perry A. A review of recently described genetic alterations in central nervous system tumors. Human pathology. 2020;96:56-66.

35. Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee SU. Glioblastoma multiforme: a review of its epidemiology and pathogenesis through clinical presentation and treatment. Asian Pacific journal of cancer prevention: APJCP. 2017;18(1):3.

36. Katz SY, Cachia D, Kamiya-Matsuoka C, Olar A, Theeler B, Prado MP, Gilbert MR, Armstrong T. Ependymomas arising outside of the central nervous system: a case series and literature review. Journal of Clinical Neuroscience. 2018;47:202-7.

37. Keshavarzi M, Darijani M, Momeni F, Moradi P, Ebrahimnejad H, Masoudifar A, Mirzaei H. Molecular imaging and oral cancer diagnosis and therapy. Journal of Cellular Biochemistry. 2017;118(10):3055-60.

38. Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, Bloom J, Gurram S, Siddiqui M, Pinsky P. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. New England Journal of Medicine. 2020;382(10):917-28.

39. Welch HG, Prorok PC, O'Malley AJ, Kramer BS. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. New England Journal of Medicine. 2016;375(15):1438-47.

40. Atkin W, Wooldrage K, Parkin DM, Kralj-Hans I, MacRae E, Shah U, Duffy S, Cross AJ. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. The Lancet. 2017;389(10076):1299-311.

41. Gustavsson I, Aarnio R, Myrnäs M, Hedlund-Lindberg J, Taku O, Meiring T, Wikström I, Enroth S, Williamson A-L, Olovsson M. Clinical validation of the HPVIR high-risk HPV test on cervical samples according to the international guidelines for human papillomavirus DNA test requirements for cervical cancer screening. Virology journal. 2019;16(1):1-7.

42. Ilic D, Djulbegovic M, Jung JH, Hwang EC, Zhou Q, Cleves A, Agoritsas T, Dahm P. Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. bmj. 2018;362:k3519.

43. Novellis P, Alloisio M, Vanni E, Bottoni E, Cariboni U, Veronesi G. Robotic lung cancer surgery: review of experience and costs. Journal of visualized surgery. 2017;3.

44. Sullivan R, Alatise OI, Anderson BO, Audisio R, Autier P, Aggarwal A, Balch C, Brennan MF, Dare A, D'Cruz A. Global cancer surgery: delivering safe, affordable, and timely cancer surgery. The lancet oncology. 2015;16(11):1193-224.

45. Zhao J, van Mierlo K, Gómez Ramírez J, Kim H, Pilgrim C, Pessaux P, Rensen S, van der Stok E, Schaap F, Soubrane O. Systematic review of the influence of chemotherapy associated liver injury on

outcome after partial hepatectomy for colorectal liver metastases. British Journal of Surgery. 2017;104(8):990-1002.

46. Holcomb GW. Thoracoscopic surgery for esophageal atresia. Pediatric surgery international. 2017;33(4):475-81.

47. Thomson P, Goodson M, Cocks K, Turner J. Interventional laser surgery for oral potentially malignant disorders: a longitudinal patient cohort study. International journal of oral and maxillofacial surgery. 2017;46(3):337-42.

48. Lee SY, Lee NR, Cho DH, Kim JS. Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation. Oncology letters. 2017;14(1):73-8.

49. He Z, Liu P, Zhang S, Yan J, Wang M, Cai Z, Wang J, Dong Y. A Freezing-Induced Turn-On Imaging Modality for Real-Time Monitoring of Cancer Cells in Cryosurgery. Angewandte Chemie International Edition. 2019;58(12):3834-7.

50. Sahiner B, Pezeshk A, Hadjiiski LM, Wang X, Drukker K, Cha KH, Summers RM, Giger ML. Deep learning in medical imaging and radiation therapy. Medical physics. 2019;46(1):e1-e36.

51. Edmund JM, Nyholm T. A review of substitute CT generation for MRI-only radiation therapy. Radiation Oncology. 2017;12(1):28.

52. Au K, Ngan RK, Ng AW, Poon DM, Ng W, Yuen K, Lee VH, Tung SY, Chan AT, Sze HC. Treatment outcomes of nasopharyngeal carcinoma in modern era after intensity modulated radiotherapy (IMRT) in Hong Kong: a report of 3328 patients (HKNPCSG 1301 study). Oral oncology. 2018;77:16-21.

53. Grover S, Harkenrider MM, Cho LP, Erickson B, Small C, Small Jr W, Viswanathan AN. Image guided cervical brachytherapy: 2014 survey of the American Brachytherapy Society. International Journal of Radiation Oncology* Biology* Physics. 2016;94(3):598-604.

54. Higuchi Y, Matsuda S, Serizawa T. Gamma knife radiosurgery in movement disorders: Indications and limitations. Movement disorders. 2017;32(1):28-35.

55. da Silva WC, de Araujo VE, dos Santos JBR, da Silva MRR, Almeida PHRF, de Assis Acurcio F, Godman B, Kurdi A, Cherchiglia ML, Andrade EIG. Comparative effectiveness and safety of monoclonal antibodies (bevacizumab, cetuximab, and panitumumab) in combination with chemotherapy for metastatic colorectal cancer: A systematic review and meta-analysis. BioDrugs. 2018;32(6):585-606.

56. Monk BJ, Mas Lopez L, Zarba JJ, Oaknin A, Tarpin C, Termrungruanglert W, Alber JA, Ding J, Stutts MW, Pandite LN. Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. Journal of Clinical Oncology. 2010;28(22):3562-9.

57. VanderMolen KM, McCulloch W, Pearce CJ, Oberlies NH. Romidepsin (Istodax, NSC 630176, FR901228, FK228, depsipeptide): a natural product recently approved for cutaneous T-cell lymphoma. The Journal of antibiotics. 2011;64(8):525-31.

58. Chu RL, Post DE, Khuri FR, Van Meir EG. Use of replicating oncolytic adenoviruses in combination therapy for cancer. Clinical Cancer Research. 2004;10(16):5299-312.

59. Khalil DN, Smith EL, Brentjens RJ, Wolchok JD. The future of cancer treatment:

Vol. 18(4) 2085-2102, October 2024, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2024.4.53

immunomodulation, CARs and combination immunotherapy. Nature reviews Clinical oncology. 2016;13(5):273-90.

60. Bommareddy PK, Patel A, Hossain S, Kaufman HL. Talimogene laherparepvec (T-VEC) and other oncolytic viruses for the treatment of melanoma. American journal of clinical dermatology. 2017;18(1):1-15.

61. Lu B, Yang M, Wang Q. Interleukin-33 in tumorigenesis, tumor immune evasion, and cancer immunotherapy. Journal of molecular medicine. 2016;94(5):535-43.

62. Hellerstedt BA, Pienta KJ. The current state of hormonal therapy for prostate cancer. CA: a cancer journal for clinicians. 2002;52(3):154-79.

63. Virgo KS, Basch E, Loblaw DA, Oliver TK, Rumble RB, Carducci MA, Nordquist L, Taplin M-E, Winquist E, Singer EA. Second-line hormonal therapy for men with chemotherapy-naïve, castration-resistant prostate cancer: American Society of Clinical Oncology provisional clinical opinion. Journal of Clinical Oncology. 2017;35(17):1952-64.

64. Eggemann H, Altmann U, Costa S-D, Ignatov A. Survival benefit of tamoxifen and aromatase inhibitor in male and female breast cancer. Journal of cancer research and clinical oncology. 2018;144(2):337-41.

65. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, Ritchie AW, Amos CL, Gilson C, Jones RJ. Abiraterone for prostate cancer not previously treated with hormone therapy. New England Journal of Medicine. 2017;377(4):338-51.

66. Wallis CJ, Klaassen Z, Bhindi B, Goldberg H, Chandrasekar T, Farrell AM, Boorjian SA, Kulkarni GS, Karnes RJ, Satkunasivam R. Comparison of abiraterone acetate and docetaxel with androgen deprivation therapy in high-risk and metastatic hormone-naive prostate cancer: a systematic review and network meta-analysis. European urology. 2018;73(6):834-44.

67. Kerckhove N, Collin A, Condé S, Chaleteix C, Pezet D, Balayssac D. Long-term effects, pathophysiological mechanisms, and risk factors of chemotherapy-induced peripheral neuropathies: a comprehensive literature review. Frontiers in pharmacology. 2017;8:86.

68. Kandula T, Park SB, Cohn RJ, Krishnan AV, Farrar MA. Pediatric chemotherapy induced peripheral neuropathy: a systematic review of current knowledge. Cancer treatment reviews. 2016;50:118-28.

69. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: a current review. Annals of neurology. 2017;81(6):772-81.

70. Shin WS, Han J, Verwilst P, Kumar R, Kim J-H, Kim JS. Cancer targeted enzymatic theranostic prodrug: precise diagnosis and chemotherapy. Bioconjugate Chemistry. 2016;27(5):1419-26.

71. Caillet P, Liuu E, Simon AR, Bonnefoy M, Guerin O, Berrut G, Lesourd B, Jeandel C, Ferry M, Rolland Y. Association between cachexia, chemotherapy and outcomes in older cancer patients: a systematic review. Clinical Nutrition. 2017;36(6):1473-82.

72. Bhatia M, Babu RS, Sonawane S, Gogate P, Girdhar A, Reddy E, Pola M. Application of nanoadsorbents for removal of lead from water. International journal of environmental science and technology. 2017;14(5):1135-54.

73. Pola M, Durthi CP, Rajulapati SB, Erva RR. Modelling and optimization of L-Asparaginase production from Bacillus stratosphericus. Current Trends in Biotechnology and Pharmacy. 2018;12(4):390-405.

74. Muller IB, Lin M, Struys EA, Heydari P, Hebing RC, Nurmohamed MT, van der Laken C, Lems WF, Cloos J, Jansen G. Development and Validation of a Sensitive UHPLC-MS/MS–Based Method for the Analysis of Folylpolyglutamate Synthetase Enzymatic Activity in Peripheral Blood Mononuclear Cells: Application in Rheumatoid Arthritis and Leukemia Patients. Therapeutic drug monitoring. 2019;41(5):598-606.

75. Birru B, Durthi CP, Kacham S, Pola M, Rajulapati SB, Parcha SR, Kamal MA. Stem Cells in Tumour Microenvironment Aid in Prolonged Survival Rate of Cancer Cells and Developed Drug Resistance: Major Challenge in Osteosarcoma Treatment. Current Drug Metabolism. 2020;21(1):44-52.

76. Tang Y, Wang Y, Kiani MF, Wang B. Classification, treatment strategy, and associated drug resistance in breast cancer. Clinical breast cancer. 2016;16(5):335-43.

77. Laetitia G, Sven S, Fabrice J. Combinatorial therapies in thyroid cancer: an overview of preclinical and clinical progresses. Cells. 2020;9(4):830.

78. Li F, Zhao C, Wang L. Molecular-targeted agents combination therapy for cancer: developments and potentials. International journal of cancer. 2014;134(6):1257-69.

79. Mokhtari RB, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, Yeger H. Combination therapy in combating cancer. Oncotarget. 2017;8(23):38022.

80. de Oliveira Júnior RG, Adrielly AFC, da Silva Almeida JRG, Grougnet R, Thiéry V, Picot L. Sensitization of tumor cells to chemotherapy by natural products: A systematic review of preclinical data and molecular mechanisms. Fitoterapia. 2018;129:383-400.

81. Ahmad T, Sarwar R, Iqbal A, Bashir U, Farooq U, Halim SA, Khan A, Al-Harrasi A. Recent advances in combinatorial cancer therapy via multifunctionalized gold nanoparticles. Nanomedicine. 2020;15(12):1221-37.

82. Bozic I, Reiter JG, Allen B, Antal T, Chatterjee K, Shah P, Moon YS, Yaqubie A, Kelly N, Le DT. Evolutionary dynamics of cancer in response to targeted combination therapy. elife. 2013;2:e00747.

83. Clarke DM, Baust JM, Van Buskirk RG, Baust JG. Chemo-cryo combination therapy: an adjunctive model for the treatment of prostate cancer. Cryobiology. 2001;42(4):274-85.

84. Mokhtari RB, Kumar S, Islam SS, Yazdanpanah M, Adeli K, Cutz E, Yeger H. Combination of carbonic anhydrase inhibitor, acetazolamide, and sulforaphane, reduces the viability and growth of bronchial carcinoid cell lines. BMC cancer. 2013;13(1):378.

85. Borriello A, Naviglio S, Bencivenga D, Caldarelli I, Tramontano A, Speranza MC, Stampone E, Sapio L, Negri A, Oliva A. Histone deacetylase inhibitors increase [p27. sup. Kip1] by affecting its ubiquitin-dependent degradation through Skp2 downregulation. Oxidative Medicine and Cellular Longevity. 2015;2015.

86. Frew AJ, Lindemann RK, Martin BP, Clarke CJ, Sharkey J, Anthony DA, Banks K-M, Haynes NM, Gangatirkar P, Stanley K. Combination therapy of established cancer using a histone deacetylase inhibitor and a TRAIL receptor agonist. Proceedings of the National Academy of Sciences. 2008;105(32):11317-22.

87. Grant S, Easley C, Kirkpatrick P. Vorinostat. Nature Publishing Group; 2007.

88. Yee AJ, Raje NS. Panobinostat and mul-

tiple myeloma in 2018. The oncologist. 2018;23(5):516.

89. Suraweera A, O'Byrne KJ, Richard DJ. Combination therapy with histone deacetylase inhibitors (HDACi) for the treatment of cancer: achieving the full therapeutic potential of HDACi. Frontiers in oncology. 2018;8:92.

90. Jones SF, Infante JR, Spigel DR, Peacock NW, Thompson DS, Greco FA, McCulloch W, Burris III HA. Phase 1 results from a study of romidepsin in combination with gemcitabine in patients with advanced solid tumors. Cancer investigation. 2012;30(6):481-6.

91. Aftab BT, Dobromilskaya I, Liu JO, Rudin CM. Itraconazole inhibits angiogenesis and tumor growth in non–small cell lung cancer. Cancer research. 2011;71(21):6764-72.

92. Rudin CM, Brahmer JR, Juergens RA, Hann CL, Ettinger DS, Sebree R, Smith R, Aftab BT, Huang P, Liu JO. Phase 2 study of pemetrexed and itraconazole as second-line therapy for metastatic nonsquamous non–small-cell lung cancer. Journal of Thoracic Oncology. 2013;8(5):619-23.

93. Tsubamoto H, Sonoda T, Ikuta S, Tani S, Inoue K, Yamanaka N. Combination chemotherapy with itraconazole for treating metastatic pancreatic cancer in the second-line or additional setting. Anticancer research. 2015;35(7):4191-6.

94. Yue GG-L, Kwok H-F, Lee JK-M, Jiang L, Wong EC-W, Gao S, Wong H-L, Li L, Chan K-M, Leung P-C. Combined therapy using bevacizumab and turmeric ethanolic extract (with absorbable curcumin) exhibited beneficial efficacy in colon cancer mice. Pharmacological research. 2016;111:43-57.

95. Kato T, Seto T, Nishio M, Goto K, Atagi S, Hosomi Y, Yamamoto N, Hida T, Maemondo M, Nakagawa K. Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR mutation–positive nonsquamous non-small cell lung cancer (NSCLC): An open-label randomized trial. American Society of Clinical Oncology; 2014.

96. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, Juan T, Sikorski R, Suggs S, Radinsky R. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. 2008.

97. Quinn BA, Dash R, Sarkar S, Azab B, Bhoopathi P, Das SK, Emdad L, Wei J, Pellecchia M, Sarkar D. Pancreatic cancer combination therapy using a BH3 mimetic and a synthetic tetracycline. Cancer research. 2015;75(11):2305-15.

98. Feldmann G, Dhara S, Fendrich V, Bedja D, Beaty R, Mullendore M, Karikari C, Alvarez H, Iacobuzio-Donahue C, Jimeno A. Blockade of hedgehog signaling inhibits pancreatic cancer invasion and metastases: a new paradigm for combination therapy in solid cancers. Cancer research. 2007;67(5):2187-96.

99. Han H, Valdepérez D, Jin Q, Yang B, Li Z, Wu Y, Pelaz B, Parak WJ, Ji J. Dual enzymatic reaction-assisted gemcitabine delivery systems for programmed pancreatic cancer therapy. Acs Nano. 2017;11(2):1281-91.

100. Kaladhar DS, Sai PC, Rao PVN. Towards an understating of signal transduction protein interaction networks. Bioinformation. 2012;8(9):437.

101. Svgk Dowluru K, Chandra Sai P, Venkata Nageswara Rao P, Govinda Rao D, Varahala Rao V, Suresh P, Rajeswara Reddy E, Vinod Kumar D, Bhaskar Reddy G. Protein interaction networks in metallo proteins

Vol. 18(4) 2085-2102, October 2024, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2024.4.53

and docking approaches of metallic compounds with TIMP and MMP in control of MAPK pathway. Letters in Drug Design & Discovery. 2013;10(1):49-55.

102. Kerbel RS. Human tumor xenografts as predictive preclinical models for anticancer drug activity in humans: better than commonly perceived—but they can be improved. Cancer biology & therapy. 2003;2(sup1):133-8.

103. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. New England journal of medicine. 2007;357(26):2666-76.

104. Cascinu S, Berardi R, Labianca R, Siena S, Falcone A, Aitini E, Barni S, Di Costanzo F, Dapretto E, Tonini G. Cetuximab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin alone in patients with advanced pancreatic cancer: a randomised, multicentre, phase II trial. The lancet oncology. 2008;9(1):39-44.

105. da Cunha Santos G, Dhani N, Tu D, Chin K, Ludkovski O, Kamel-Reid S, Squire J, Parulekar W, Moore MJ, Tsao MS. Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: National Cancer Institute of Canada Clinical Trials Group Study PA. 3. Cancer. 2010;116(24):5599-607.

106. Altomare I, Bendell JC, Bullock KE, Uronis HE, Morse MA, Hsu SD, Zafar SY, Blobe GC, Pang H, Honeycutt W. A phase II trial of bevacizumab plus everolimus for patients with refractory metastatic colorectal cancer. The oncologist. 2011;16(8):1131.

107. Chen LL, Gouw L, Sabripour M, Hwu W-J, Benjamin RS. Combining targeted therapy with immunotherapy (interferon-α) Rational, efficacy in gastrointestinal stromal tumor model and implications in other malignancies. Oncoimmunology. 2012;1(5):773-6.

108. Israelsen WJ, Vander Heiden MG, editors. Pyruvate kinase: function, regulation and role in cancer. Seminars in cell & developmental biology; 2015: Elsevier.

109. Bhullar KS, Lagarón NO, McGowan EM, Parmar I, Jha A, Hubbard BP, Rupasinghe HV. Kinase-targeted cancer therapies: progress, challenges and future directions. Molecular cancer. 2018;17(1):1-20.

110. Ricciuti B, Lamberti G, Andrini E, Genova C, De Giglio A, Bianconi V, Sahebkar A, Chiari R, Pirro M, editors. Antibody–drug conjugates for lung cancer in the era of personalized oncology. Seminars in Cancer Biology; 2019: Elsevier.

111. Sarfraz I, Rasul A, Hussain G, Hussain SM, Ahmad M, Nageen B, Jabeen F, Selamoglu Z, Ali M. Malic enzyme 2 as a potential therapeutic drug target for cancer. IUBMB life. 2018;70(11):1076-83.

112. Wen D, Liu D, Tang J, Dong L, Liu Y, Tao Z, Wan J, Gao D, Wang L, Sun H. Malic enzyme 1 induces epithelial–mesenchymal transition and indicates poor prognosis in hepatocellular carcinoma. Tumor Biology. 2015;36(8):6211-21.

113. Hsieh J-Y, Li S-Y, Tsai W-C, Liu J-H, Lin C-L, Liu G-Y, Hung H-C. A small-molecule inhibitor suppresses the tumor-associated mitochondrial NAD (P)+-dependent malic enzyme (ME2) and induces cellular senescence. Oncotarget. 2015;6(24):20084.

114. Zhang X, Jiang L, Huang K, Fang C, Li J, Yang J, Li H, Ruan X, Wang P, Mo M. Site-Selective Phosphoglycerate Mutase 1 Acetylation by a Small Molecule. ACS Chemical Biology. 2020;15(3):632-9.