RECURRENCE OF CANCER WITH LONG TERM SIDE EFFECTS OF CANCER TREATMENT

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ABSTRACT
The review describes the recurrence of cancer and all the possible late complications of cancer treatment. Radiation therapy, radioiodine therapy and some chemotherapy have life threatening long-term side effects that are responsible for secondary cancer. Improper and chronic injection of cancer treatment from radiation therapy, radioiodine therapy, and some chemotherapy agents (alkylating agents, anthracyclines, topoisomerase (II) inhibitors, streptozotocin, chlorozotocin, diethylstilbesterol, tamoxifen, cis-platin, etc.) can also the major risk of recurrence of cancer. Genetic predisposition and estrogen-progestin therapy is also found to make individual more susceptible to recurrence of cancer.

KEYWORDS: Radiotherapy, radioiodine therapy, chemotherapy, hormone therapy, secondary cancer, recurrence of cancer.

INTRODUCTION
In recent years more and more people are surviving cancer today. Cancer survivors can be affected by a number of health problems but often their greatest concern is facing recurrence of cancer. Recurrence of cancer can be related with past cancer or some cancer survivors may develop a new and unrelated cancer later. This is called a secondary cancer in the same organ or nearby the affected organ. This may be because the whole organ and sometimes nearby tissues were exposed to the various anti-cancer therapies (radiation therapy, radioiodine therapy, some chemotherapy, etc.) and all the possible late complications of cancer treatment developing a secondary cancer. Late effects of cancer therapy are very serious trouble and
some common long term effects are cognitive effects, hair loss, hearing loss, lung damage, heart damage, loss of fertility, long term psychological effects, hypothyroidism, hyperthyroidism, dental abnormalities, vision problems, osteoporosis, etc. Moreover, these therapies were recognized as a potential cause of secondary cancer for example leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia, lymphocytic leukemia, testicular cancer, osteosarcoma, breast cancer, thyroid cancer, myelodysplastic syndrome, a bone marrow cancer that can turn into acute leukemia. Most often, these cancers develop after 5-10 years of chemotherapy, radiation therapy and radioiodine therapy treatment. The risk of secondary cancer after anti-cancer therapy depends on the dose of radiation, the area treated, the age of patient, higher drug doses, longer treatment time, and higher dose-intensity, etc. Chemotherapy is known to be a greater risk factor for recurrence of leukemia than radiation therapy.[1-6]

RADIATION THERAPY
In fact, more than half people with cancer will get radiation as a part of their cancer treatment. When radiation damages genes of a cancerous cell, then cell can’t grow and can’t divide more. This means radiation can be used to kill cancerous cells and to shrink tumors. The selection of radiation depends on type of tissues and a doctor specially trained to treat cancer patients with radiation. But on the other hand, we have some side effects of radiation therapy which depend on the area of the body being treated, amount of radiation that reached to affected tissues, how long it took to give the dose and age of the patient. The early effects of radiation therapy may be seen after a few days or few weeks after treatments have started and may go on for several weeks after treatments have ended. Retired radiation therapy is recognized as a potential cause of recurrence of cancer e.g. acute myelogenous leukaemia (AML), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), a bone marrow disorder that can turn into acute leukemia, myelodysplastic syndrome (MDS), solid tumors (e.g. lung cancer, thyroid cancer, bone sarcoma, and gastrointestinal or stomach cancers), etc. The area treated with radiation therapy is very susceptible, because these cancers tend to develop in or near the area that was treated with radiation therapy. Some organs such as breast and thyroid, seem to be more likely to develop cancers after radiation therapy than other organs.[1]
RADIOIODINE THERAPY
Thyroid cancer is a metastasized and curable by radioiodine therapy with $^{131}$I. The main indication for administering repeated doses of $^{131}$I is the appearance of abnormal uptake in a whole body scan following diagnostic or therapeutic $^{131}$I administration. Our body will give off radiation for some time after we get radioiodine therapy depending on the dose of radioiodine used and where we are being treated. Radioiodine therapy also have some side effects e.g. tenderness & swelling of neck and salivary glands, nausea, vomiting, dry mouth, taste changes, etc. Patients who had radioiodine therapy may have increased risk of developing leukemia after treatment. Doctors disagree on exactly how much the risk is increased but most of the largest studies have found that this is an extremely rare complication.\[^7-8^\]

CHEMOTHERAPY
In chemotherapy, the drugs enter in bloodstream and therefore reach all parts of the body. This means the drugs travel throughout the body to interact cancer cells wherever they are. Now a large number of chemotherapeutic drugs are used either alone or in combination with other drugs or treatments. Chemotherapeutic drugs demolish cancer cells by damaging them so they can’t divide and grow more. These drugs can also impair the normal cells due to this behaviour of these drugs. It may cause some common side effects including the risk of secondary cancers e.g. acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), acute lymphocytic leukemia (ALL), testicular cancer and some solid malignant tumors. Cancer patients have higher risk of cancer with higher drug doses, longer treatment period and higher dose intensity. Some chemotherapy drugs are given below which show carcinogenic behaviour in humans.

Alkylating agents
It is a type of chemotherapeutic drugs are used to treat various types of cancers including leukemia, lymphoma, Hodgkin’s disease, multiple myeloma, sarcoma, lung, breast, ovary cancer, etc. Few of them chemotherapeutic drugs can show common and many delayed side effects including increase the risk of leukemia, acute myelogenous leukemia (AML)\[^9,10^\] and long term damage the bone marrow.\[^9,11^\]
Melphalan (Alkeran)
Patients treated with melphalan for breast cancer, ovarian cancer, and bone marrow cancer (multiple myeloma) has an increased risk of leukaemia. The risk of leukaemia increased with increasing dose of melphalan. It is listed by IARC in group of “known to be a human carcinogen”. Epidemiological studies found that the treatment of melphalan has some common and rare side effects because of the way this drug acts on DNA.[12]

Mechlorethamine (Chlormethine)
Mechlorethamine has higher risk of recurrence of cancer after treatment especially when such therapy is combined with other anti-neoplastic agents or radiation therapy. Cases have been reported secondary leukaemia and Hodgkin’s disease in patients treated with drug mechlorethamine with or without radiation therapy. It is listed in by IARC in group of “Reasonable anticipated being a human carcinogen”. IARC noted that although there were numerous case reports of cancer following treatment with mechlorethamine but the patients had also been treated with radiation or other drugs. Lung cancer risk increased significantly with increasing cumulative dose of mechlorethamine.[13]
**Chlorambucil (Leukeran)**

Treatment of chlorambucil either alone or in combination with other therapies has some common and rare side effects but these side effects can not affect everyone who has chlorambucil treatment and may be different if patient having more than one type of chemotherapy. It causes bone-marrow suppression (neutropenia, anemia, and thrombocytopenia) which is the most commonly occurring side effect. Chronic treatment with chlorambucil has been associated with the development of acute non-lymphocytic leukaemia. Risk of leukemia increased with increasing dose and duration of treatment. It is listed by IARC in group of “known to be a human carcinogen”.[14]

**cyclophosphamide (endoxan/cytophosphane)**

Cyclophosphamide treatment has life-threatening adverse effects, especially at higher doses, it cause acute myeloid leukaemia, urinary-bladder cancer, and permanent infertility. It is listed by IARC in group of “known to be a human carcinogen”. A case-control study in Germany found that the risk of leukaemia increased with increasing dose of cyclophosphamide. More recently, a nested case-control study of non-Hodgkin’s lymphoma patients reported that the risk of urinary-bladder cancer increased with increasing cumulative dose of cyclophosphamide.[15,16]

**Semustine (methyl-CCNU, MeCCNU)**

It is listed by IARC in group of “known to be a human carcinogen”. Chemotherapy treatment of semustine shows some common and rare side effects including delayed effects of secondary cancer. An increased relative risk for non-lymphocytic leukaemia was found among patients with gastrointestinal cancer who were treated with semustine. Epidemiological studies show that the risk of leukaemia increased with increasing cumulative dose of semustine.[17]

**Lomustine (CCNU or CeeNU)**

Chemotherapy treatment of lomustine has severe and life-threatening effects. These effects vary person to person; some people have very few side effects while others may experience more. There is a slight risk of developing blood cancer such as leukaemia years after taking lomustine.[18] It is listed by IARC in group of “Reasonably anticipated to be a human carcinogen”.
**Carmustine (BCNU)**
Carmustine is used to treat Hodgkin’s disease, non-Hodgkin’s lymphoma, multiple myeloma, primary or metastatic brain tumors, malignant melanoma, breast cancer, gastrointestinal cancer, Ewing’s sarcoma, and Burkitt’s lymphoma. Treatment of carmustine can show some common and other side effects including bone marrow and pulmonary toxicities. It also causes secondary cancer of acute nonlymphocytic leukaemia.\[17\] It is listed by IARC in group of “Reasonably expected to be a human carcinogen”.

**Prednimustine**
Prednimustine is used in the treatment of various malignancies, chronic lymphatic leukaemia, non-Hodgkin's lymphomas and breast cancer. But the IARC listed it in the group of reasonable expected to be a carcinogen. Chemotherapy treatment by prednimustine, either alone or combination with other chemotherapeutic drugs, has some common and rare side effects such as damage to white blood cells, platelets fluid retention, high glucose and low chance of getting secondary cancer.\[9\]

**Busulfan (Bulsufex/Myleran)**
Busulfan is used to treat polycythaemia vera, myelofibrosis, primary thrombo-cythaemia, and chronic myelogenous leukaemia but improper and chronic use of busulfan have some common and rare side effects e.g. pulmonary fibrosis, hyper-pigmentation, seizures, hepatic (veno-occlusive disease), wasting syndrome, thrombocytopenia, a condition of lowered blood platelet count and acute myeloid leukaemia develops in patients who have previously treated with busulfan. The IARC listed it in a group of “known to be a human carcinogen”.\[19\]

**Treosulfan (Dihydroxybusulfan)**
Treosulfan is used to treat ovarian cancer, haematological malignancies, malignant melanoma, breast cancer, bone-marrow ablation before stem cell transplantation, and show clinical activity against some other solid tumours. Sometimes, chemotherapy section of treosulfan shows severe and life-threatening adverse effects of recurrence of cancer. IARC listed it in group of “known to be a human carcinogen”.\[20\]

**Thiotepa (N, N’N’-triethylene-thio-phosphoramide)**
Chemotherapy treatment of thiotepa has some common and rare side effects. Adamson and Seiber summarized nine case reports from 1970 to 1978 of development of non-lymphocytic leukaemia in patients with primary cancer at other sites, who had received only
thiotepa as a therapeutic agent. Additional evidence was provided by a case-control study which found that patients treated with thiotepa were significantly more likely to develop secondary leukaemia. Therefore, thiotepa was listed in a group of “known to be a human carcinogen” by IARC. It is also used in combination chemotherapy with cyclophosphamide in patients with refractory malignancies treated with autologous bone transplantation.[21]

**Procarbazine (Idicarb)**

Procarbazine is an alkylating chemotherapy drug for the treatment of glioblastoma multiforme and hodgking’s lymphoma. Chemotherapy treatment with procarbazine also increases the risk of recurrence of acute myloid leukemia and myelodysplastic syndrome.[5]

**Anthracyclines**

A class of cancer chemotherapy drugs called anthracyclines, it is first isolated from the pigment of *Streptomyces peucetius*. Anthracyclines are used to treat many cancer sites *e.g.* uterine, leukemias, lymphomas, breast, lung and ovarian cancer. Chronic administration of anthracyclines (*e.g.* doxorubicin (DOX), daunorubicin (DNR), and epirubicin (Ellence)) has long term side effects including cardiomyopathy, congestive heart failure, and sometimes blood cancer such as leukemia. Leukemia can appear years after taking high doses or many doses of DOX, DNR and epirubicin cytotoxic regimens.[22]

**Topoisomerase-II inhibitors**

A class of chemotherapeutic drugs called topoisomerase-II inhibitors. Some of them have been found to cause leukemia mainly acute myelogenous leukemia (AML). Most cases are found within 2 or 3 years after treatment. Etoposide, teniposide, and mitoxantrone are reported here as example of this class.[23]
Etoposide (Etoposide phosphate/VP-16/Etopophos)
Etoposide is an antineoplastic, cytotoxic drug which is used to treat various types of cancer e.g. Ewing’s sarcoma, Kaposi’s sarcoma, lung cancer, testicular cancer, lymphoma, nonlymphocytic leukemia, and glioblastoma multiforme in adult and children. Some time it is also used in a conditioning regimen prior to a bone marrow or blood stem cell transplant. Chronic injection of etoposide with combination of bleomycin and cis-platin was found to be a human carcinogen causing acute myeloid leukaemia after treatment, but there is no sufficient evidence to draw a separate conclusion about the carcinogenicity of etoposide alone. According to IARC, it is listed in group of “known to be a human carcinogen”. [24-25]

Teniposide
Teniposide is used in the treatment of adult and childhood acute lymphocytic leukaemia (ALL), brain tumours, neuroblastoma, small-cell & non-small-cell lung cancer, lymphomas and bladder cancer. Long term effects of teniposide are medical problems that recurrence of cancer after treatment ends. According to IARC, it is listed as a reasonably expected to be a human carcinogen.[26]

Mitoxantrone
Mitoxantrone is used in the treatment of breast cancer, non-Hodgkin’s lymphoma, ovarian cancer, prostate cancer, lung cancer and certain leukaemia but the chemotherapy treatment of mitoxantrone also has some long term side effects after completion of treatment. The side effects of mitoxantrone and their asperity depend on how much this drug is given. Normally, side effects are common (found in greater than 30%) for patients taking it, some delayed effects as interference with the pumping action of the heart and slight risk of developing a blood cancer of leukemia. The IARC listed it in a group of “known to be a human carcinogen”. [27-28]
Streptozotocin
Streptozotocin is used for treatment of pancreatic islet-cell cancer, pancreatic adenocarcinoma, Hodgkin’s disease, colorectal cancer, liver cancer, (hepato-cellular carcinoma), adrenal gland cancer (pheochromocytoma), lung cancer (epidermoid carcinoma), lymphocytic lymphoma, Burkitt’s lymphoma, acute lymphocytic leukemia, malignant melanoma, metastatic sarcoma, and malignant carcinoid tumors. But the chemotherapy treatment of Streptozotocin has slight risk of getting secondary tumor. It is in 1981 listed by IARC in group of “reasonably expected to be a carcinogen”. The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to streptozotocin. But sufficient data are available to cause tumor in experimental animals by streptozotocin caused tumors at several different tissue sites in rats and mice.[29]

Chlorozotocin
Chlorozotocin is used to treat melanoma, multiple myeloma, stomach cancer, large intestine cancer, pancreas cancer, and lung cancer. On the other hand, the chemotherapy treatment of Chlorozotocin has some common and rare side effects including getting secondary cancer. IARC listed it in a group of “reasonably expected to be a carcinogen”. Exposure to chlorozotocin in laboratory animals caused tumor at different tissue sites in male rats.[30]

Diethylstilbestrol (DES / Stilboestrol)
Diethylstilbestrol is known to be a human carcinogen based on sufficient evidence of carcinogenicity in humans. Exposure to diethylstilbestrol also increased the risk of secondary cancer. IARC included it in a group of “known to be a carcinoma”. [31]

Tamoxifen
It is commonly used as a primary therapy for breast cancer in elderly women who are considered poor candidates for surgery. It has been tested as a possible treatment for other types of cancer e.g. melanoma, liver cancer (hepatocellular carcinoma), kidney (renal-cell carcinoma), pancreas (adenocarcinoma), stomach, cervix of the uterus, and ovary. Further, it is not widely used for these purposes because treatment of this drug has slight risk of secondary endometrial cancer. Due to these observations, it is listed by IARC in a group of “known to be a carcinogen”. [32]
**Cis-platin**

The metal based anti-cancer drug *cis*-platin are one of the important drugs in clinical use. Its importance is reflected by the fact that it is estimated 50-70% cancer patients are treated with platinum drugs. It is used to treat a lots of different cancers *e.g.* lung, testicular, ovarian, breast, prostate, and almost all the most common types of tumor.

* cis-platin is not an alkylating agent, but it attacks on cancer cells in much the same way and have delayed side effects including risk of leukaemia too. But the risk of developing leukaemia after treatment with *cis*-platin is not as great as with the alkylating agents. The risk of leukaemia rises as the higher and improper dose of drug used and if radiation is given along with the *cis*-platin.

**Genetic predisposition to cancer**

Evidences show that large number of cancer types are caused not only by environmental factors but also caused by hereditary predispositions. For example, lung cancer is in most instances related to smoking, and mortality from lung cancer has been shown to be four time greater among non-smoking relatives (siblings and parents) of the lung cancer patients than smoking relatives. Less than 10% of cancer patients have inherited mutations that predispose to cancer, and the frequency is even lower (0.1%) for certain type of tumors.

Some cancer patients have inherited gene changes (mutations) that increase the chances of getting secondary cancer. But overall, these inherited changes are relatively uncommon. Single inherited mutant gene may be enough to cause a very high cancer risk. Hereditary mutations (also called germ line mutations) are gene defected that pass from a parent to child. Because the mutation is present at the beginning, it exists in all cells of the body, including reproductive cells. This means the mutation can be passed from generation to generation.
hereditary mutation is a major factor in about 5% to 10% of all cancers. Some people are more likely to develop cancer than others simply because they are born with mutations in their genes.\textsuperscript{[35]}

**HORMONE THERAPY**

**Estrogen-progestin therapy (EPT)**

According to Women’s Health Initiative (WHI) study, the women taking estrogen-progestin therapy (EPT) which have a higher risk of developing breast cancer and lower risk of getting colorectal cancer compared with those who didn’t take hormones. To put this into numbers, if 10,000 women took estrogen-progestin therapy for a year, this would add up to about 8 more cases of breast cancer per year than if they had not taken hormone therapy (HT). The longer HT was used, the more the risk will be increased.

**Estrogen therapy (ET)**

Using systemic estrogen therapy (estrogen as a pill, patch, or the high-dose) has been shown to increase the risk of endometrial cancer (cancer of the lining of the uterus). The risk remains higher than average even after estrogen therapy is no longer used.\textsuperscript{[35-36]}

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**REFERENCE**


