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Research Paper

Alkylating agents induced secondary malignancies – A review

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ABSTRACT
Cytotoxic therapies can be associated with side effects, some of which are immediate and others are delayed in onset and progress to form second malignancies in cancer survivors. Normal cells are at risk for mutations in DNA, carcinogenesis and a secondary malignancy due to the effects of chemotherapy as it damages the DNA and disrupt the cell division process of both cancer and normal cells. The alkylating agents, topoisomerase II agents, and anthracyclines are chemotherapy agents reported to be carcinogenic. Alkylating agents are used to treat many types of cancers and it is said to have a marked effect on myeloid cells which leads to the development of leukemia. Several studies have shown that alkylating agents are rising the risk of solid tumors. Increased risk is associated with the combination of radiotherapy.
Key words: *Chemotherapy, Alkylating agents, Secondary malignancies, Solid tumors*

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I. INTRODUCTION

Advances in chemotherapy and radiotherapy have greatly impacted the outcome of certain cancers. These cytotoxic therapies can be associated with side effects, some of which are immediate and others which are delayed in onset (1). Progress of a second malignancy is one of the most devastating late effects of both childhood and adult onset cancers on survivors (2). Secondary cancer can be detected as a histologically distinct malignancy that develops at least 2 months after primary cancer treatment is completed (3). Not all patients have the same risk of developing a second cancer and not all secondary malignancies are caused by treatment with chemotherapy (4). Genetic factors and acquired conditions linked to treatment modalities are contributing factors of the development of secondary malignancy. Genetic factors include Li-Fraumeni syndrome (LFS) and retinoblastoma. Radiation and chemotherapy have been confirmed to be the most strongly associated with the development of secondary malignancy in terms of the acquired factors (3).

Chemotherapy kills cancer cells by destroying DNA and disrupting the division of cells, which also affects the normal cells that cause latent DNA damage (5,6). Cellular defects therefore have the ability to permanently interrupt DNA replication and transcription. If the defects are not effectively repaired, the fundamental change in the molecule of DNA may result in cellular death, mutation and evolving carcinogenesis. When normal cells are unable to recover from the cytotoxic effects, transformation, and mutation of normal cells also occur. Cells with a high rate of growth factor such as bone marrow cells, gastrointestinal lining and hair follicles are more susceptible to the effects of chemotherapy. These normal cells are at risk for mutations in DNA, carcinogenesis and a secondary malignancy. The alkylating agents, topoisomerase II agents, and anthracyclines are chemotherapy agents reported to be carcinogenic. In treating patients with Hodgkin's and non-Hodgkin's lymphomas (NHL), breast and ovarian cancer, brain tumors, and chronic leukemia, alkylating agents are indicated (4). Most of the effectively investigated alkylating agents are carcinogenic in experimental animals and humans, and are proven human carcinogens (7). These agents have a marked effect on myeloid cells which leads to the development of leukemia (4). Acute myeloid leukemia (AML), sarcoma, lung cancer, stomach cancer, pancreatic cancer, colorectal cancer and thyroid cancer have been associated with elevated risks. Increased risks after alkylating chemotherapy have been reported for gastrointestinal tract cancers only in patients who have underwent radiotherapy (8). This review will address the associations between the alkylating agents and specific secondary malignancies, as derived from studies in humans.

Alkylating agents

Alkylating agents are the most commonly used anticancer medications and are main components of combination chemotherapy (9). They are used in cancer treatment where an alkyl group (C_nH_{2n+1}) is attaches to DNA. The alkyl group is attached to the DNA guanine base, at the purine ring's number 7 nitrogen atom (10). They can be classifed into six categories as shown in Table 1. They are nitrogen mustards, nitrosoureas, alkyl sulfonates, triazines, ethylenimines and methylhydrazines.

Mechanism of action

Alkylating agents work by inhibiting DNA transcription into RNA and thus stopping the synthesis of the proteins. They replace alkyl groups with hydrogen atoms on DNA, resulting in the formation of cross links within the DNA chain resulting in cytotoxic, mutagenic and carcinogenic effects. This action takes place in all cells, but alkylating agents have their primary effect on the rapidly dividing cells which have no time for DNA repair. Cancer cells are among the most affected, since they are among the most rapidly dividing cells. The end result of the alkylation process leads to misreading of the DNA code and inhibiting DNA, RNA, and protein synthesis, and causing programmed cell death (apoptosis) in tumor cells that are rapidly proliferating. Hematopoetic, reproductive, and endothelial cells, however, also rapidly divide which accounts for the common side effects of alkylating agents: anemia, pancytopenia, amenorrhea, impaired spermatogenesis, intestinal mucosal damage, alopecia, and increased risk of malignancy leading to secondary cancers (11).

Leukemia

Leukemia is the most common confirmed malignancy among patients treated with chemotherapy (7). Treatment for solid tumors, such as Hodgkin's disease, Ewing sarcoma, and rhabdomyosarcoma, is correlated with a dose-response relationship for alkylating agents, and leukemia risk. Alkylating agents increase the risk of leukemia almost 5-fold, but that risk increases to almost 24-fold in patients receiving the highest doses (12). Initial indications of acute leukemia occur in patients treated with alkylating agents, making it clear that this form of oncogenesis is a major complication of alkylating agent therapy. Several reports suggest that in patients, the risk of acute leukemia following alkylating agent therapy could be 10% or higher (13). Busulfan, carmustine, chlorambucil, cyclophosphamide, dihydroxybusulfan, lomustine, mechlorethamine, melphalan, prednimustine, and semustine are alkylating agents that cause human leukemia. After treatment with alkylating agents, leukemia risk starts to increase at 1 to 2 years, peaks at 5 to 10 years and then decreases (14). The most potent oncogenic agents tend to be procarbazine and other methylating agents and melphalan tends to produce a higher incidence of acute leukaemia than cyclophosphamide (15,16). Cyclophosphamide's lesser leukemogenic potential may well be connected to this agent's hematopoietic stem cell-sparing effect. Although there are still insufficient data available to be certain, high-dose alkylating agent therapy given in intermittent pulses over a relatively short period of time appears to be less oncogenic than prolonged alkylating agent therapy (17).

Lukemia caused by the most common alkylating agents is secondary acute myeloid leukaemia (s-AML), which may appear years after stopping the therapy. Alkylating agent induced s-AML is often accompanied by myelodysplastic syndrome (MDS), with chromosome 5 or 7 loss or deletion (18). During the early 1970s, many researchers reported an excess risk of s-AML in adults and children with Hodgkin lymphoma (HL) who received chemotherapy or related alkylating agent regimens combined with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) (19). Chemotherapeutic agents related to the production of leukemia following testicular cancer include cisplatin and etoposide (2). Even host factors tend to play a crucial role in the production of s-AML induced by alkylating agent. For example, in individuals with neurofibromatosis 1 who develop a first cancer, a high occurrence of second malignancies like s-AML has been reported. Increased susceptibility to s-AML was confirmed in Nf1 knockout mice in patients with neurofibromatosis 1 who were previously treated with alkylating agents (20). Patients with other genetic syndromes, such as Fanconi anemia, also display susceptibility to alkylating agent induced s-AML and MDS, as do individuals with genetic polymorphisms that affect glutathione transferase theta 1 function (21).

Lung cancer

Lung cancer is the most common secondary malignancy following treatment for HL. Both alkylating chemotherapy and irradiation are associated with a 10 times higher relative risk of lung cancer (22). In a large international case-control study of lung cancer after HL, taking into account the roles of radiation exposure and the amount of tobacco usage, a clear dose-response relationship between the lung cancer was found to increase the cumulative dose of either mechlorethamine or procarbazine, and with the number of alkylating agent chemotherapy cycles, a class that included not only mechlorethamine or procarbazine but also other agents (23). Other research, though not as well controlled for radiation and tobacco use, showed similar findings for the administration of alkylating agents and the risk of subsequent lung cancer (2).

Tobacco use is an important influencing factor following HL for treatment of induced lung cancer. In the international case-control research of lung cancer after HL, patients who received either alkylating agent chemotherapy alone or 5 or more Gy of radiation therapy alone in the area of the lung in which cancer originated increased the risk of lung cancer 4.3-fold and 7.2-fold respectively, compared to patients with minimal treatment exposures and who were non-smokers or light smokers. These relative risks in patients who also smoked at least one pack of cigarettes a day increased to 16.8-fold and 20.2-fold, respectively. The relative risk of subsequent lung cancer was nearly 50-fold for cigarette smoking (at least one pack per day) even given alkylating agent chemotherapy and ≥5 Gy of radiation therapy to the region of the lung in which cancer formed (23,24). Further research showed that these results were consistent with the smoking and treatment multiplicative effects (2).

Urinary bladder cancer

Secondary bladder cancer attributable to treatment with cyclophosphamide is a major issue in patients treated for other forms of malignancies or for other benign diseases (25). In the early 1970's, the first human case of urinary bladder cancer attributed to exposure to cyclophosphamide was identified (26). Since then numerous studies on this phenomenon have been published. Cyclophosphamide is a prodrug that requires cytochrome enzyme P450 bioactivation to exert its cytotoxic impact. Phosphoramide is the principal active cytotoxic component of the three major binding components of DNA (phosphoramide mustard, nornitrogen mustard and acrolein). The presumed mechanism of action is DNA alkylation resulting in DNA cleavage, and DNA strands and DNA proteins cross-linkage (25). In a large cohort of 2 year NHL survivors, Travis et al quantified the risk of bladder cancer following cyclophosphamide therapy. Radiotherapy given without cyclophosphamide was associated with a non-significant increased risk of malignant bladder. Excessive risk of bladder cancer after treatment with both radiotherapy and cyclophosphamide was as predicted when individual risks were summed up. The authors concluded that the risk of developing an induced bladder cancer with cyclophosphamide depends on the cumulative dose of cyclophosphamide. In patients treated with combined doses of up to 20 g, the relative risk of developing secondary bladder cancer is about 2. In patients treated with cumulative doses between 20 and 50 g, the relative risk rises to about 6, and is even higher in patients treated with cumulative doses of cyclophosphamide above 50 g (27). Kaldor et al obtained similar results in a case-controlled collaborative group study on women receiving treatment for ovarian cancer. Another finding from their case control study is the association of bladder tumours with alkylating chemotherapeutic agents other than cyclophosphamide, especially melphalan and thiotepa. In women treated with these chemotherapeutic drugs, the relative risk of bladder tumours was above 4. The increased risk was limited to the community of pelvic radiotherapy-treated women. When given in combination with pelvic radiotherapy, an association has been found between bladder tumours and other alkylating chemotherapeutic agents such as melphalan and thiotepa (28).

Osteosarcoma

Alkylating agents, as used with radiation therapy, can also potentiate the risk of secondary bone cancers. The relative risk of secondary bone sarcomas following radiation therapy was 2.7 but the relative risk increased to 4.7 when alkylating agents were also used (29). Three cases of osteosarcoma developed several years after the primary malignancies according to a study conducted by Shimatani et al. This may be attributed to alkylating agents (ifosfamide and cyclophosphamide) and a topoisomerase II inhibitor (etoposide) that had been administered for the primary cancer. Chondroblastic and osteoblastic osteosarcoma are mostly induced secondary osteosarcoma due to alkylating agents that are administered for HL and medulloblastoma treatment (3).

Thyroid cancers

Cancer therapy can impair normal thyroid function in a number of ways (1). New studies provide evidence of increased risk of thyroid cancer in patients receiving radiation doses of up to 20 Gy associated with alkylating agents (30). Adult HL patients have a nine fold probability of developing thyroid cancer attributable to alkylating agents (4). The most frequently occurring secondary thyroid cancer is papillary thyroid carcinoma (1). The risk tends to increase with alkylator level, with a highly significant risk in highest category exposed (30). Hypothalamic, pituitary or thyroid function may be affected by cytotoxic chemotherapy. They can intensify a thyroid autoimmune process leading to dysfunction (1). Combinations of drugs (alkylating agents, anthracyclines and/or bleomycin) did not raise the risk beyond the alkylating agents alone (30).

Breast cancer

Several studies among adolescent / adult HL survivors have shown that alkylating chemotherapy in combination with chest radiotherapy significantly reduces the risk of breast cancer that was due to premature

menopause induced chemotherapy. A novel finding however is that alkylating agents and chemotherapy containing anthracycline were associated in a dose dependent manner with increased risk of breast cancer. Henderson et al was the first to demonstrate increased risk of breast cancer in the absence of chest radiation following exposure to anthracyclines and alkylating agents (31).

II. CONCLUSION

It seems that the causal associations between chemotherapy with alkylating agents and secondary malignancies have been identified. Many studies have shown that alkylating agents are rising the risk of secondary malignancies. The risk and benefit of alkylating agents can be outweighed before initiating the therapy. More studies are needed to confirm the relationship of these agents in cancer patients to develop new cancers.

REFERENCES

[1]. Sai-Ching JY, Alice CC, Rena VS and Robert FG: The endocrine effects of nonhormonal antineoplastic therapy. Endocr Rev 19(2): 144–172, 1998.

[2]. Andrea KN, Lisa BK, Ethel SB and Lois BT: Secondary malignancies across the age spectrum. Semin Radiat Oncol 20(1): 1-20, 2010. DOI:10.1016/j.semradonc.2009.09.002.

[3]. Akiyoshi S, Masanari A, Manabu H, Naoto O, Tadashi I, Naoki T, Junichi H, Chika N and Hiroaki N: Secondary osteosarcoma in patients previously treated for childhood cancer: three case reports. Mol Clin Oncol 10: 153-158, 2019. DOI: 10.3892/mco.2018.1752.

[4]. Teri VS: Chemotherapy-induced secondary malignancies. J Infus Nurs 26(6): 353-361, 2003.

[5]. Vicki B: Tracking Chemotherapy's Effects on Secondary Cancers. J Natl Cancer Inst Monogr 105(19): 1421–1422, 2013.

[6]. Weaver CH: Therapy Related or "Secondary Malignancies" and New Cancers. Cancer Connect, 2019. Available at https://news.cancerconnect.com/treatment-care/therapy-related-or-secondary-malignancies-and-new-cancers-3qqPvjA8uUSxj6Xn8YgfeA. Last accessed on 3rd September 2020.

[7]. Paolo B and John MK: Secondary malignancies following cancer chemotherapy. Acta Oncol 33(6): 591-598, 1994. DOI:10.3109/02841869409121767.

[8]. Flora EV and Cecile MR: Anthracyclines and Alkylating Agents: New risk factors for breast cancer in childhood cancer survivors? J Clin Oncol 34(9): 891-894, 2016.

[9]. Alok CB, Kanchan V, Sukh MS and Bharat BA: Pathways Linked to Cancer Chemoresistance and Their Targeting by Nutraceuticals. Role of Nutraceuticals in Chemoresistance to Cancer, pp 1-30, 2018. DOI: 10.1016/B978-0-12-812373-7.00001-2.

[10]. Alkylating Agents. *US National Library of Medicine, 2014. Available at* https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/alkylating-agent. Last accessed on 3rd September 2020.

[11]. Alkylating Agents LiverTox: Clinical and Research Information on Drug-Induced Liver Injury, 2015. Available at https://www.ncbi.nlm.nih.gov/books/NBK547849/. Last accessed on 3rd September 2020.

[12]. Hawkins MM , Kinnier Wilson LM , Stovall MA, Marsden HB, Potok MHN, Kingston JE and Chessells JM: Epipodophyllotoxins, alkylating agents, and radiation and risk of secondary leukaemia after childhood cancer. Br Med J 304: 951–958, 1992.

[13]. Einhorn N: Acute leukemia after chemotherapy (melphalan). Cancer 41: 444, 1978.

[14]. Debra LF: Secondary cancers in cancer survivors. Supportive oncology, pp 456-463, 2011.

[15]. Dorr FA, Coltman CA: Second cancers following antineoplastic therapy. Curr Probl Cancer 9(2): 1-43, 1985. DOI: 10.1016/s0147-0272(85)80033-7.

[16]. Green MH, Harris EL, Gershenson DM, Malkasian GD, Melton LJ, Dembo AJ, Bennett JM, Moloney WC and Boice JD: Melphalan may be a more potent leukemogen than cyclophosphamide. Ann Intern Med 105(3): 360-367, 1986. DOI: 10.7326/0003-4819-105-3-360.

[17]. Colvin M: Alkylating agents. Holland-Frei Cancer Medicine (6th edition), pp 110-119, 2003.

[18]. Davies SM: Therapy-related leukemia associated with alkylating agents. Med Pediatr Oncol 36(5): 536-540, 2001. DOI: 10.1002/mpo.1126.

[19]. Hijiya N, Ness KK, Ribeiro RC and Hudson MM: Acute Leukemia as a Secondary Malignancy in Children and Adolescents. Cancer 115: 23-35, 2009. DOI: 10.1002/cncr:23988.

[20]. Mahgoub N, Taylor BR, Le Beau MM, Gratiot M, Carlson KM, Atwater SK, Jacks T and Shannon KM: Myeloid malignancies induced by alkylating agents in Nf1 mice. Blood 93(11): 3617-3623, 1999. PMID: 10339466.

[21]. Chen H, Sandler DP, Taylor JA, Shore DL, Liu E , Bloomfield CD, Bellet DA: Increased risk for myelodysplastic syndromes in individuals with glutathione transferase theta 1 (GSTT1) gene defect. Lancet 347(8997): 295-297, 1996. DOI: 10.1016/s0140-6736(96)90468-7.

[22]. Lash BW: Which secondary cancers are possible complications of Hodgkin lymphoma (Hodgkin disease) therapy? Medscape 2018. Available at https://www.medscape.com/answers/201886-107010/which-secondary-cancers-are-possible-complications-of-hodgkin-lymphoma-hodgkin-disease-therapy. Last accessed on 3rd September 2020.

[23]. Travis LB, Gospodarowicz M, Curtis RE, Clarke EA, Andersson M, Glimelius B, Joensuu T, Lynch CF, van Leeuwen FE, Holowaty E, Storm H, Glimelius I, Pukkala E, Stovall M, Fraumeni JF, Boice DJ and Gilbert E: Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 94(3): 182–192, 2002. DOI: 10.1093/jnci/94.3.182.

[24]. Gilbert ES, Stovall M, Gospodarowicz M, van Leeuwen FE, Andersson M, Glimelius B, Joensuu T, Lynch CF, Curtis RE, Holowaty E, Storm H, Pukkala E, van't Veer B, Fraumeni JF, Boice DJ, Clarke EA and Travis LB: Lung cancer after treatment for Hodgkin's disease: focus on radiation effects. Radiat Res 159(2):161–173, 2003. DOI: 10.2307/3580824.

[25]. Nilsson S and Ullen A: Chemotherapy-induced bladder cancer. Scand J Urol Nephrol 42(218): 89-92, 2008. DOI: 10.1080/03008880802291832.

[26]. Worth PH: Cyclophosphamide and bladder. Br Med J 3(5767): 182, 1971. DOI: 10.1136/bmj.3.5767.182-a.

[27]. Travis LB, Curtis RE, Glimelius B, Holowaty EJ, Van Leeuwen FE, Lynch CF, Hagenbeek A, Stovall M, Banks PM and Adami J: Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. J Natl Cancer Inst 87(7):/524-530, 1995. DOI: 10.1093/jnci/87.7.524.

[28]. Kaldor JM, Day NE, Kittelmann B, Pettersson F, Langmark F, Pedersen D, Prior P, Neal F, Karjalainen S and Bell J: Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: a case control study. Int J Cancer/63(1):/1-6, 1995. DOI: 10.1002/ijc.2910630102.
[29]. Rheingold SR, Neugut AI and Meadows AT: Therapy-Related Secondary Cancers. Holland-Frei Cancer Medicine (6th edition), pp 120-126, 2003.
[30]. Veiga LHS, Bhatti P, Ronckers CM, Sigurdson AJ, Stovall M, Smith SA, Weathers R, Leisenring W, Mertens AC, Hammond S, Neglia JP, Meadows AT, Donaldson SS, Sklar CA, Friedman DL, Robison LL and Inskip PD: Chemotherapy and thyroid cancer risk: A report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev 21(1): 92–101, 2012. DOI: 10.1158/1055-9965.
[31]. Henderson TO, Moskowitz CS, Chou JF, Bradbury AR, Neglia JP, Dang CT, Onel K, Friedman DN, Bhatia S, Strong LC, Stovall M, Kenney LB, Barnea D, Lorenzi E, Hammond S, Leisenring WM, Robison LL, Armstrong GT, Diller LR and Oeffinger KC: Breast cancer risk in childhood cancer survivors without a history of chest radiotherapy: A report from the childhood cancer survivor study. J Clin Oncol 34(9): 910–918, 2016.DOI: 10.1200/JCO.2015.62.3314.

Table 1: Classification of alkylating agents

Alkylating agents

Nitrogen mustards	Cyclophosphamide Mechlorethamine Ifosfamide Melphalan Chlorambucil
Nitrosoureas	Streptozocin Carmustine Lomustine
Alkyl sulfonates	Busulfan
Triazines	Dacarbazine Temozolomide
Ethylenimines	Thiotepa Altretamine
Methylhydrazines	Procarbazine

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