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Original Research Article

The Effect of Chemotherapy in the Childhood Cancer Survivor Study Cohort on the Probability of Subsequent Malignant Neoplasms

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Abstract:

Background: Over time, the use of therapeutic radiation for the treatment of children cancer has decreased, corresponding with an increase in the use of chemotherapy. Few studies have been done on the possibility of developing malignant neoplasms (SMNs) after treatment.

Methods: In 2004 to 2020, survivors diagnosed before age 21 were followed up on SMNs diagnosed more than five years after diagnosis (excluding nonmelanoma skin cancers). The following treatments were used to determine the standardized incidence ratios (SIRs) and cumulative incidence of SMN: radiation only (n = 20), chemotherapy + radiation (n = 104), chemotherapy alone (n = 74), or neither (n = 21). Chemotherapy-associated SMN risk, including dose-response correlations, was evaluated using multivariable models.

Results: Of the 221 survivors in the cohort, 74 underwent chemotherapy alone, 104 underwent radiation therapy in addition to chemotherapy, 20 underwent radiation therapy alone, and 21 underwent neither. After 166 person-years, 3 secondary malignant neoplasms (SMNs) were discovered in 20 survivors who had only had chemotherapy, with 27% of these cases occurring in survivors of osteosarcoma. The 15-year cumulative incidence of SMN was 3.9%, with survivors of osteosarcoma and Hodgkin lymphoma having the highest incidence. For chemotherapy alone, chemotherapy plus radiation, radiation without chemotherapy, and neither chemotherapy nor radiation, the cumulative loads were 4.3, 9.7, 12.1 and 3.6 per 100 individuals, respectively.

Conclusion: SMN is more common in pediatric cancer survivors who only had chemotherapy, particularly in those who got higher cumulative doses of alkylating agents and platinum. It was discovered that the dosage responses for alkylating agents and SMN rates, as well as anthracyclines and breast cancer rates, were linear. By minimizing cumulative doses and considering other chemotherapies, the risk of SMN may be reduced.

Introduction

After a pediatric cancer diagnosis, malignant neoplasms (SMNs) significantly increase morbidity and death. The incidence and risk factors of SMN have been reported in earlier studies on pediatric cancer survivors [1]. The greatest SMN risk is invariably associated with therapeutic radiation. This favorable outcome can be attributed, at least in part, to the gradual reduction in the administered dosage of therapeutic radiation. Procarbazine, platinum-based compounds, and alkylating agents have been found to be effective in the treatment of gastrointestinal malignancies. Alkylating agents have also shown efficacy in the management of carcinomas. Furthermore, the combination of alkylating agents and anthracyclines has demonstrated positive outcomes in patients with breast cancer [3]. Alkylating agents and epipodophyllotoxins with leukemia; anthracyclines and alkylating agents with sarcoma. These findings have limited generalizability because they are restricted to specific underlying malignancies, specific SMN types, or individuals who received both radiation and chemotherapy. The risk for SMNs in people receiving chemotherapy alone has to be further investigated because chemotherapy kinds and doses have altered. The current study investigated connections between chemotherapy and SMN in the large and diverse North Bihar Pediatric cancer survivor cohort of nonirradiated, long-term pediatric cancer survivors.

Materials and Methods

Population

The childhood cancer survivors who were diagnosed at North Bihar Population between 2004-2019, are included in the study cohort. Leukemia, non-Hodgkin lymphoma, Wilms, neuroblastoma, STS, or bone cancer affected patients younger than 21. Before recruiting participants, centers obtained authorization from

the human subjects committee and informed consent from parents or those under the age of 18. At death or last contact before November 30, 2019, respondents were censored following a baseline and up to five follow-up questions.

Finding SMNs and the Treatment Exposures

The health records of consenting participants were reviewed for cumulative dosages of chemotherapeutic medicines five years following diagnosis. The cumulative doses of alkylating agents are CED [4], the cumulative doses of anthracyclines are the doxorubicin isotoxic equivalent dose [20], and the cumulative platinum doses are calculated [5]. The maximum radiation exposure for each patient was calculated for eight different body parts. Pathology report review, or both validated SMNs following self or proxy report or death certificate, or, if unavailable, medical records, or the death certificate. Pathologists and oncologists looked into SMNs separately.

Statistical Methods

Four treatment groups that were mutually exclusive were created for childhood cancer survivors: radiation and no chemotherapy, radiation and chemotherapy, chemotherapy plus Radiotherapy, and no chemotherapy and no radiation. By combining all cohort events throughout the specified period of time, time from diagnosis was used as the time scale, and fatalities were considered competing risk events, the cumulative incidence and burden of SMNs were investigated. Even in cases when the original cancer diagnosis and treatment are colinear, multivariable models were exclusively tuned for chemotherapy.

Results

Of the 221 survivors, 74 underwent chemotherapy alone, 104 underwent radiation therapy in addition to chemotherapy, 20 underwent radiation therapy alone, and 21 underwent neither. Among the cohort of survivors who exclusively underwent chemotherapy, approximately 50% were of the female gender and had been diagnosed with pediatric malignancies prior to reaching the age of five. Leukemia, osteosarcoma, and non-Hodgkin lymphoma were the most commonly observed primary diagnoses, with a median follow-up duration of 15 years.

After 166 person-years, 3 SMNs were discovered in 20 survivors who had just received chemotherapy. In survivors of osteosarcoma, 27% of SMNs occurred in the chemotherapy-only group. The incidence of SMN during a 15-year period was 3.9%, with survivors of osteosarcoma and Hodgkin lymphoma showing the greatest rates. In the context of therapeutic interventions, namely chemotherapy alone, chemotherapy combined with radiation, radiation therapy without chemotherapy, and the absence of both chemotherapy and radiation, the cumulative burdens of secondary malignant neoplasms (SMNs) over a span of 15 years were observed to be 4.3, 9.7, 12.1, and 3.6 per 100 individuals, respectively.

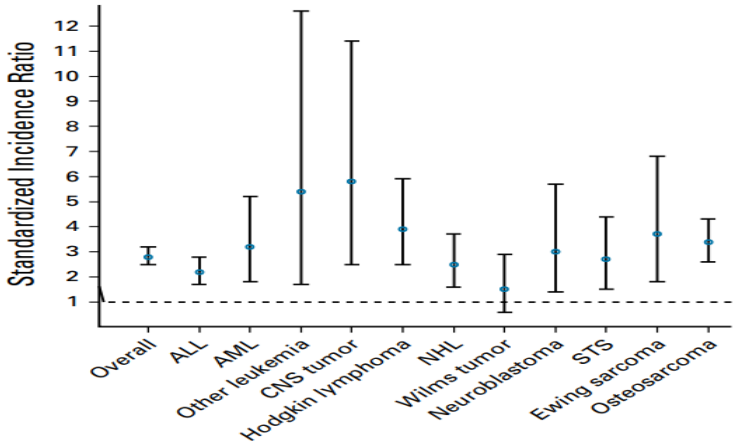

Figure 1: 95% confidence intervals (CIs) and normalized incidence ratios for recurring malignancies by childhood cancer diagnosis among the chemotherapy-only group. Soft-tissue sarcoma (STS), non-Hodgkin lymphoma (NHL), and acute myelogenous leukemia (AML) are the acronyms for these diseases.

With an AER of 1.0 per 1,000 person-years among survivors of CNS tumors, the SMN rate for chemotherapy survivors was almost three times higher than that of the general population. Higher survival rates were seen in leukemia/lymphoma, sarcoma, and neuroblastoma patients. The greatest SMN rates for nonrecurrent soft tissue sarcoma (8.5), breast cancer (5.2), and thyroid cancer (4.8) were seen in chemotherapy-treated sarcoma survivors. Following CNS cancers (1.6) and osteosarcoma (2.4), survivors without chemotherapy or radiation had higher standardized incidence ratios (SIRs).

The SMN rate was linked to high cumulative exposure to platinum, high cumulative exposure to alkylating agents, and female sex. The 5-year therapy period had nothing to do with it. Among survivors of chemotherapy alone, multivariable

analysis revealed a higher incidence of soft tissue sarcoma, breast, thyroid, and melanoma SMN types. For breast cancer, a dose-response relationship was shown to be linear, with a dose-response of 300 mg/m². SMN types were unaffected by cumulative dose or chemotherapy classes.

More higher SIRs and AERs were observed with therapeutic radiation with chemotherapy than with chemotherapy alone. Radiation or chemotherapy-free survivors still had a higher risk than the general population, but their SMN rates were lower. SMN rates were also associated in a multivariable study of radiation and chemotherapy survivors with female sex and high-dose alkylating agent exposure. In this group, platinum exposure had no effect on SMN rates.

Discussion

The utilization of therapeutic radiation has witnessed a decline due to the emergence of persistent health complications. Furthermore, there have been modifications in the recommended chemotherapeutic interventions, encompassing alterations in both the nature of the agents employed and the prescribed dosages. In the realm of pediatric oncology, it has been observed that the probability of being diagnosed with a SMN in survivors has exhibited a downward trend, concomitant with the advancements made in cancer therapies. The inquiry regarding the potential association between chemotherapy without radiation and an elevated occurrence of SMN has not garnered substantial scrutiny in the medical literature [6,7]. In a well-characterized group of childhood cancer survivors, it has been observed that individuals who were exclusively treated with chemotherapy exhibit an elevated susceptibility to the development of subsequent malignant neoplasms (SMNs) when compared to the general population. Nevertheless, the aforementioned risk is approximately 50% lower in comparison to individuals who have undergone a combination of radiation therapy and chemotherapy [8]. A linear dose-response relationship has been observed between the cumulative amount of alkylating agents and the relative rate of SMN [6]. Additionally, it has been observed that individuals who received higher cumulative amounts of alkylating agents and/or platinum-based medications exhibited increased rates of secondary malignant neoplasms (SMNs). The association between being exposed to anthracyclines and the development of breast cancer has been duly substantiated. The outcomes of the alkylating agent, nevertheless, were not replicated, presumably due to heterogeneity within the study cohort. In line with the findings of the present study, Henderson et al. [8] conducted an investigation into the prospective susceptibility to breast cancer among female survivors of childhood cancer who did not receive chest radiation therapy. A four-fold elevation in the risk of breast cancer, surpassing that observed in the general population, was identified. This heightened risk was found to be associated with being exposed to anthracyclines and alkylating agents, with the degree of risk being directly proportional to the dosage of alkylating agents administered.

The present study revealed a notable association between exposure to high-dose alkylating agents and platinum agents, and an increased occurrence of secondary malignant neoplasms (SMN). This association was particularly prominent among survivors who solely underwent chemotherapy treatment. Considering the prevalent utilization of platinum therapy in the management protocols for sarcomas and central nervous system tumors, it is plausible to hypothesize that the association between platinum exposure and the elevated incidence of Li Fraumeni-associated malignancies can be elucidated [7]. Additional noteworthy correlations between chemotherapy and renal SMNs and sarcoma have been found in survivors of irradiation, underscoring the necessity of more research on chemotherapeutic risk factors for SMNs.

In summary, this study lends credence to the idea that chemotherapy raises the incidence of SMN, although hereditary susceptibility to cancer might also be involved. In order to ascertain the associations between specific types of secondary malignant neoplasm (SMN) and chemotherapy agents, as well as to comprehend the disparities in SMN incidence between individuals who underwent chemotherapy and those who did not, collaboration with other substantial cohorts of pediatric cancer survivors is imperative.

Conclusion

In summary, survivors of chemotherapy-only treatment within the cohort are at higher risk of emerging secondary malignant neoplasms (SMNs), particularly when alkylating agent or platinum doses are higher. Additionally, we discovered a dose-response correlation between the incidence of breast cancer after anthracycline exposure. These results highlight the significance of early SMN surveillance and risk-based counseling for persons receiving chemotherapy, particularly those without radiotherapy and with greater cumulative doses of alkylating agents and platinum. To identify precise chemotherapeutic dose thresholds for surveillance recommendations and investigate genetic vulnerability to SMN development, more research is required. Working together, pediatric cancer survivor cohorts can provide insight into the effects of different SMN types and chemotherapeutic exposures.

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