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The Cyclophosphamide Equivalent Dose as an Approach for Quantifying Alkylating Agent Exposure. A Report from the Childhood Cancer Survivor Study

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Abstract

BACKGROUND—Estimation of the risk of adverse long-term outcomes such as second malignant neoplasms and infertility often requires reproducible quantification of exposures. The method for quantification should be easily utilized and valid across different study populations. The widely used Alkylating Agent Dose (AAD) score is derived from the drug dose distribution of the study population and thus cannot be used for comparisons across populations as each will have a unique distribution of drug doses.

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METHODS—We compared the performance of the Cyclophosphamide Equivalent Dose (CED), a unit for quantifying alkylating agent exposure independent of study population, to the AAD. Comparisons included associations from three Childhood Cancer Survivor Study (CCSS) outcome analyses, receiver operator characteristic (ROC) curves and goodness of fit based on the Akaike's Information Criterion (AIC).

RESULTS—The CED and AAD performed essentially identically in analyses of risk for pregnancy among the partners of male CCSS participants, risk for adverse dental outcomes among all CCSS participants and risk for premature menopause among female CCSS participants, based on similar associations, lack of statistically significant differences between the areas under the ROC curves and similar model fit values for the AIC between models including the two measures of exposure.

CONCLUSION—The CED is easily calculated, facilitating its use for patient counseling. It is independent of the drug dose distribution of a particular patient population, a characteristic that will allow direct comparisons of outcomes among epidemiological cohorts. We recommend the use of the CED in future research assessing cumulative alkylating agent exposure.

Keywords

late effects of cancer treatment; chemotherapy; long term survival; cyclophosphamide; alkylating agent; alkylating agent dose score

BACKGROUND AND RATIONALE

Evaluation of late effects of treatment has assumed increasing importance as the number of long-term survivors has grown. This is particularly important for cancer patients diagnosed at younger ages where the majority are expected to survive for many years after diagnosis [1].

Critical to the assessment of these late effects is a reproducible system for quantitation of therapeutic exposures. Radiation exposures can be readily quantitated using standard designations for radiation units, although evaluation of the impact of a dose that varies by target volume can be complex. Consideration of the impact of chemotherapeutic agent exposures is more difficult due to the absence of systems that specify equivalent doses of different agents within the same drug class.

Alkylating agents are widely used for the treatment of cancers of children and adolescents and are associated with a number of late adverse effects of treatment including second malignant neoplasms [2, 3], male [4] and female [5] infertility, ovarian failure [6], and premature menopause [7, 8]. The Alkylating Agent Dose (AAD) score was developed for two case-control studies conducted by the Late Effects Study Group (LESG) [9, 10]. For each alkylating agent, the total dose per square meter was summed for each patient. The dose distribution for each agent was divided into tertiles. A patient who did not receive a particular agent received a score of zero for that particular agent. If the patient's dose was within the first tertile, a score of one was assigned; if within the second tertile, a score of two was assigned; and if within the third tertile, a score of three was assigned. The scores for an individual patient were summed and the resulting sum was the AAD for that patient [10]. In the study of alkylating agent exposure and secondary leukemia, scores ranged from zero to 12 [10] and in the study of secondary bone sarcomas, the range was from zero to nine [9]. The ranges for the tertiles for each of the two studies were not reported, but were derived from the dose distributions of the two different patient populations (secondary leukemia and secondary leukemia controls; secondary bone sarcoma and secondary bone sarcoma controls). This score could not be compared between the two LESG studies. The AAD has

been extensively used in research conducted over the past 20 years to quantify alkylating agent exposure despite the limitation of being cohort-specific, which has precluded comparison of results across studies of different cohorts.

The present project was undertaken to develop a simple, cohort-independent method for normalizing alkylating agent exposure to units of a single drug. We reviewed published studies in which the acute hematological toxicity of various alkylating agents could be compared, developed an algorithm for determining the Cyclophosphamide Equivalent Dose (CED) and evaluated the performance of the CED in three analyses of data from the Childhood Cancer Survivor Study (CCSS) previously analyzed using the AAD [4, 8, 11].

PATIENTS AND METHODS

The CCSS cohort consists of previously untreated patients diagnosed prior to 21 years of age with leukemia, lymphoma, central nervous system cancer, neuroblastoma, bone or soft tissue sarcoma, or kidney cancer, who survived for at least five years after the date of diagnosis. Survivors were diagnosed between January 1, 1970 and December 31, 1986 at one of 26 participating institutions. The study design, cohort characteristics and outcomes ascertained are presented in detail elsewhere [12–14]. The CCSS was approved by the Institutional Review Board at each participating institution, and informed consent for participation was obtained from all subjects who were 18 or more years of age, or their parents, if the subject was less than 18 years of age.

EXPOSURE ASSESSMENT

Following receipt of a signed medical release, a trained clinical research associate at each participating CCSS institution conducted a comprehensive medical record abstraction of chemotherapy, surgery, and radiotherapy (RT) using a standardized procedure. Data regarding the chemotherapeutic agents administered to the patient for treatment of the original cancer, and for any recurrences of the cancer, including the cumulative dose of drug administered for drugs of interest, were abstracted from the medical records of 12,954 participants [14]. Details of the RT dosimetry methods are described in Stovall et al. [15, 16]. The current analyses focusing on alkylating agent exposure included adjustment for RT exposures for the specific outcomes of interest (i.e., testes, ovaries, hypothalamic/pituitary region (HP) and jaw).

Cyclophosphamide Equivalent Dose Calculation

The Cyclophosphamide Equivalent Dose is calculated using the following equation: $CED (mg/m^2) = 1.0 (\text{cumulative cyclophosphamide dose } (mg/m^2)) + 0.244 (\text{cumulative ifosfamide dose } (mg/m^2)) + 0.857 (\text{cumulative procarbazine dose } (mg/m^2)) + 14.286 (\text{cumulative chlorambucil dose } (mg/m^2)) + 15.0 (\text{cumulative BCNU dose } (mg/m^2)) + 16.0 (\text{cumulative CCNU dose } (mg/m^2)) + 40 (\text{cumulative melphalan dose } (mg/m^2)) + 50 (\text{cumulative Thio-TEPA dose } (mg/m^2)) + 100 (\text{cumulative nitrogen mustard dose } (mg/m^2)) + 8.823 (\text{cumulative busulfan dose } (mg/m^2))$

The medical literature between 1946 and July 13, 2012 was searched using OVID Medline and the following alkylating agents in pairs combined with the search term “randomized trial (English, human)”: BCNU (carmustine), busulfan, CCNU (lomustine), chlorambucil, cyclophosphamide, ifosfamide, melphalan, nitrogen mustard, procarbazine, Thio-TEPA (thiotepa). We excluded articles which were reviews, those which included hematopoietic stem cell transplantation as a component of the treatment regimen, those in which the randomized element was not an alkylating agent (e.g. immunotherapy [17], colony stimulating factors [18], parenteral nutrition [19], radiation therapy [20]), and those which

randomized between two regimens that differed by more than replacement of a single alkylating agent with another (e.g. MACOP-B versus ProMACE-MOPP [21], ProMACE-CytaBOM versus ProMACE-MOPP [22], BCVPP versus MOPP [23], CCNU, cyclophosphamide, methotrexate versus cyclophosphamide, methotrexate [24]) (Supplementary Table I). The search was supplemented with manuscripts within the reference lists of the literature identified through the search and data from non-randomized studies when no randomized study was available. Hematological toxicity was chosen as the basis for comparison because it was evaluated and graded in most studies and could be compared across studies, when possible, using the criteria published by Cooper et al. [25], which map directly to the platelet and white blood cell grades in Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [26].

BCNU and CCNU were compared to nitrogen mustard in randomized trials of MOPP-like (Mustargen (nitrogen mustard), Oncovin (vincristine), procarbazine and prednisone) [25, 27, 28] four drug combinations and BCNU and procarbazine were compared in a randomized trial of the three drug combinations of BOP (BCNU, Oncovin (vincristine) and prednisone) and OPP (Oncovin (vincristine), procarbazine and prednisone). Because there were more patients previously treated with combined modality therapy and fewer previously untreated patient randomized to MOPP than to BOPP (BCNU, Oncovin (vincristine), procarbazine and prednisone), these regimens were considered to be equitoxic despite the finding of borderline significance in the increased frequency of hematological toxicity among those treated with MOPP [27] (Table I, Studies 1 – 3). The procarbazine dose utilized in OPP could not be easily converted into a dose in mg/m^2 due to the use of a dose escalation scheme at the beginning of each course. However the toxicities of MOPP in the BCNU trial and the CCNU trial were similar, with the CCNU trial using the conventional $100 \text{ mg}/\text{m}^2/\text{day} \times 14$ days dosing of procarbazine. For this reason procarbazine $1400 \text{ mg}/\text{m}^2$ was determined to be equivalent to BCNU $80 \text{ mg}/\text{m}^2$ (Table 1, Studies 1 – 3).

The comparison between chlorambucil and nitrogen mustard was based on the reported equivalence of the hematological toxicity of MVPP (Mustargen (nitrogen mustard), vinblastine, procarbazine and prednisone) and ChIVPP (chlorambucil, vinblastine, procarbazine and prednisone) [29–31] (Table I, Studies 4 – 6). The data reported by McElwain et al were not categorized to allow separation of those with grade 3 or 4 hematological toxicity [29]. The data of Cooper et al. (Table I, Study 6) are more consistent with the original report by McElwain et al. [29] than those of Druker et al. [32], suggesting that $84 \text{ mg}/\text{m}^2$ of chlorambucil was not more myelosuppressive than $12 \text{ mg}/\text{m}^2$ of nitrogen mustard. The studies of LOPP (chlorambucil, vincristine, procarbazine and prednisone) [33, 34] utilized lower doses of procarbazine and chlorambucil than were employed in the studies of ChIVPP and thus could not be utilized further in this analysis (Table I, Studies 7 – 8).

The comparison between cyclophosphamide and nitrogen mustard was based on the toxicity of the original MOPP regimen as reported by DeVita et al. [35], and of COPP (cyclophosphamide, vincristine, procarbazine and prednisone) as reported by Morgenfeld et al. [28] (Table I, Studies 9 and 10). There was no published randomized study comparing these two regimens.

Melphalan was evaluated in three studies. In Stanford trials S-2 through S-6, outcomes for those who received radiation therapy (RT) and PAVe (procarbazine, Alkeran (melphalan) and vinblastine) were compared to those of patients treated with RT and MOP(P) [36, 37] (Table I, Study 11). Melphalan was compared to cyclophosphamide [38] and to BCNU and CCNU [39] in randomized studies among patients with multiple myeloma (Table I, Studies 12 and 13).

Ifosfamide and cyclophosphamide were compared in a randomized trial of vincristine, actinomycin D and cyclophosphamide (VAC) and vincristine, actinomycin D and ifosfamide (VAI) in childhood rhabdomyosarcoma [40] (Table I, Study 14).

Cyclophosphamide and busulfan (Myleran) were compared in a double-blind, randomized trial in patients with chronic phase chronic myelocytic leukemia (CML). (Table I, Study 15) and in a three arm, randomized, placebo controlled study of post-resection adjuvant chemotherapy for lung carcinoma. The estimate based on actual median dose (Table I, Study 15) was chosen rather than the estimate based on planned total dose (Table I, Study 16) [41, 42].

Thio-tepa and nitrogen mustard were compared in a randomized phase II study in patients with advanced breast or lung cancer, Hodgkin lymphoma or malignant melanoma [43] (Table I, Study 17).

The results from those studies in Table I which were utilized to develop the dose equivalents are summarized in Table II, with the dose of each agent equivalent to 100 mg/m² of cyclophosphamide indicated in the final row of the Table. The AAD was calculated as previously reported [5, 44]. Supplementary Table II shows the drug dose distribution of the several alkylating agents in mg/m² of the original drug in the tertiles used for the AAD [5] calculation and the CED range for each of these agents in the three tertiles.

STATISTICAL METHODS

Male Fertility

Male fertility was analyzed using Cox proportional hazard models with age as the time-scale as previously described in Yasui et al. [45]. Subjects entered the risk set for regression analyses at the age at which they entered the CCSS cohort (five years after date of diagnosis of primary cancer) or age 15, whichever was older, and were followed until the minimum age of first pregnancy, death, or completion of baseline questionnaire, whichever came first. Multiple-imputation methodology for event-time imputations [46, 47] was employed for those who reported siring one or more pregnancies, but did not report their age at first pregnancy. Age at first pregnancy was available for 81.8% (770/941) of the survivors who reported siring a pregnancy; of those, 61 pregnancies that occurred less than 5 years after the date of diagnosis were excluded. Age at first pregnancy was imputed for the remaining 18.2% (49 excluded) of the male survivors.

Candidate treatment variables evaluated included CED, summed AAD score, and RT dose to the HP and testes. Actinomycin D, BCNU, CCNU, cyclophosphamide, cis-platinum, cytosine arabinoside, daunorubicin, doxorubicin, DTIC, nitrogen mustard, procarbazine, vinblastine, vincristine, VM-26 (Teniposide), VP-16 (Etoposide), thio-tepa, ifosfamide, and melphalan were evaluated individually in the fertility analysis. Univariable analyses were carried out, with final treatment variables included in the multivariable model that were significant at the 0.1 level or that markedly influenced (>10% change) the effect of another factor in the final multivariable model (confounder) [4].

Non-Surgical Premature Menopause

A multivariable Poisson regression model of treatment and other effects on the development of non-surgical premature menopause (NSPM) in survivors was constructed by a stepwise variable-selection method, using the Akaike Information Criterion (AIC) to determine the effectiveness of adding or removing each candidate variable [8]. In addition to alkylating agents (CED and summed AAD score), candidate variables included initial cancer diagnosis, age, ovarian and pelvic radiation therapy, and stem cell transplantation. Subjects were

considered to be menopausal if they had not experienced a spontaneous menses for at least six months and other causes, e.g., pregnancy; use of agents such as injectable progesterone and gonadotropin-releasing hormone analogs had been excluded [48, 49]. Subjects who had a diagnosis associated with ovarian dysfunction (e.g., Turner syndrome) ($n = 7$), never had a spontaneous menses or ceased spontaneous menstruation within the first five years following the initial cancer diagnosis (i.e., individuals with acute ovarian failure) ($n = 321$), received more than 30 Gy of RT to the brain and/or had a primary tumor in the HP region ($n = 592$), returned a questionnaire completed by someone other than the participant ($n = 712$), developed a second malignancy before the onset of menopause ($n = 391$); or whose RT data were incomplete or not available ($n = 349$) were excluded from the analysis of premature menopause. The number of person-years at risk was determined as the time between menarche and the most recent menstrual period; surgically induced menopause was treated as a censoring event in the analysis of NSPM [8].

Dental Outcomes

The dental outcomes, including the presence of hypodontia, microdontia, enamel hypoplasia, abnormal root development, 6 missing teeth, xerostomia, gingivitis, 6 cavities, denture use, oral prosthesis use or dental bridge use, and combinations of the above as “at least one dental health issue”, “at least one soft tissue issue”, and “at least one dental appliance”, were evaluated using logistic regression [11]. Odds Ratios (ORs) for associations between risk of these outcomes and radiation to the teeth, AAD score or CED, exposure to steroids, antimetabolites, and vincristine, were adjusted for age-at-study, sex, race/ethnicity, education, household income, and health insurance [11].

For each pair of models using CED vs. AAD, the Akaike Information Criterion (AIC) was used to assess and compare model fit (lower is better). Receiver operator characteristic (ROC) curves, based on the linear predictor and area under the curve (AUC), were generated to compare the utility of the CED and AAD models as prognostic factors, where the model with the greatest area under the curve has the best discriminating abilities. For the purposes of this analysis, where direct comparison between classification properties was the goal, a simplified ROC curve utilizing a binary outcome was used. Analyses were conducted using SAS (SAS Institute Inc., Cary, NC, USA) version 9.1.3 (male fertility) and the %roc macro [50], and version 9.3 (dental and premature menopause).

RESULTS

Male Fertility

The distributions of demographic and treatment variables of the males included in these analyses are shown in Supplementary Table III and were published previously [4]. The hazard ratio for siring a pregnancy is significantly associated with alkylating agent exposure in a dose-dependent manner in the multivariable models for both CED and AAD (Table III).

The AIC was 3270 for the CED model and 3546 for the AAD model indicating slightly better fit for the CED model. The AUC of the ROC for both the CED and AAD models was 0.88 and curves were superimposable, indicating that the classification properties of the two measures were virtually identical ($p = 0.14$) (Supplementary Figure 1).

Non-surgical premature menopause

The distributions of demographic and treatment variables of the females included in these analyses are shown in Supplementary Table IV and were published previously [8]. The rate ratio for non-surgical premature menopause was significantly increased with increasing alkylating agent exposure for multivariable models utilizing CED or AAD. Moreover, the

observed associations with ovarian RT, stratified on initial cancer diagnosis (Hodgkin lymphoma versus all other diagnoses) remained when applying the CED as the alkylating agent exposure metric (Table IV).

The AIC was similar for the CED (773) and for the AAD (772) model. The AUCs for both the CED and AAD models were 0.83 and ROC curve shapes were virtually identical ($p = 0.84$) (Supplementary Figure 2).

Dental Abnormalities

The distributions of demographic and treatment variables of the CCSS participants included in these analyses are shown in Supplementary Table V and were published previously [11]. The odds ratios for microdontia, hypodontia, six cavities, abnormal roots and enamel hypoplasia were increased by any dose of radiation to the teeth > 0 cGy in models that employed the CED or AAD (Table V). As observed in the earlier published analyses using AAD and cyclophosphamide alone, the CED also provided a clear dose-response relationship with increasing risk of dental abnormalities with increasing alkylating agent exposure.

The AUC of the ROCs for the dental CED and AAD models ranged from 0.60 to 0.70. None of the comparisons between the AUCs was statistically significant (Supplementary Figures 3 to 7), indicating similar discriminatory performance between CED and AAD for each of the dental outcomes.

DISCUSSION

We developed the CED because evaluation of many adverse late outcomes of treatment for cancer in children and adolescents requires a method for normalization of the cumulative doses of various alkylating agents, and because the AAD does not allow results derived from different epidemiological cohorts to be compared. We have demonstrated that the CED and AAD perform similarly when included in several models for different survivor outcomes that include treatment exposures. We chose to compare drugs based on hematological toxicity because this was the toxicity that was reported in all studies evaluated and was generally evaluated in a manner that allowed conversion of the reported toxicity data to the system developed by Cooper et al [25] which mapped to the grading of CTCAE Version 4.0 [26]. We considered the doses of the evaluated alkylating agents to be equivalent when the frequency of hematological toxicity of two regimens that differed only by the substitution of a single alkylating agent for another, such as BCNU for nitrogen mustard, was similar. In those cases where a randomized study was not available, such as a direct comparison of cyclophosphamide and nitrogen mustard, we compared the results of single arm studies conducted on comparable patient populations, recognizing that this was an imperfect substitution for a randomized study. We did not choose to evaluate and compare hematological toxicity based on the hypothesis that acute hematological toxicity predicted the presence and/or severity of any of the recognized late adverse effects of treatment with alkylating agents. Indeed the adoption of the CED may allow analyses of the relationship between acute hematological toxicity and various alkylating agent related adverse late outcomes, such as infertility and second malignant neoplasms, to be conducted in the future.

A primary advantage of the CED is its derivation from actual drug doses rather than dependence on a drug dose distribution specific to a single population, which is the basis for calculation of the AAD. This appealing attribute allows the CED to be used to compare the results of epidemiological studies from different patient cohorts. Use of the CED in both the research and clinical settings has a number of advantages. Quantification of alkylating agent exposure using the CED will permit more direct comparison of research findings across

studies and expand the potential for performing meta-analyses. Within a clinical setting, use of the CED will facilitate physicians' interactions with patients for the purpose of counseling on the risk of acute and long-term effects of alkylating agents.

CONCLUSION

In summary, we have demonstrated that the CED performs statistically in a manner that is essentially identical to the AAD. We recommend adoption of the CED for estimation of cumulative alkylating agent exposure in future outcome analyses in which alkylating agent exposure may be a significant risk factor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Details of studies reviewed to determine the alkylating agent dose equivalents

Study	Drug(s) of interest	Study Design	Study Description	Drug doses per course	Toxicity	Alkylating agent dose evaluated
1	Nitrogen mustard, BCNU [27]	Randomized	Hodgkin lymphoma MOPP (N = 104; median age, 38 years; M:F = 2.13:1.00) BOPP (N = 103; median age, 33 years; M:F = 1.56:1.00) BOP (N = 107; median age, 37 years; M:F = 1.56:1.00) OPP (N = 112; median age, 32 years; M:F = 2.13:1.00)	MOPP <ul style="list-style-type: none"> • M (Mustargen, nitrogen mustard) - 12 mg/m² • O (Oncovin, vincristine) - 2.8 mg/m² • P (procarbazine) - 50 mg, day 1, 100 mg, day 2, 100 mg/m², days 3 – 13 • P (prednisone) - 560 mg/m² BOPP <ul style="list-style-type: none"> • B (BCNU) - 80 mg/m² • O (Oncovin, vincristine) - 2.8 mg/m² • P (procarbazine) - 50 mg, day 1, 100 mg, day 2, 100 mg/m², days 3 – 13 • P (prednisone) - 560 mg/m² 	MOPP more leukopenia and thrombocytopenia (p = 0.05); MOPP grade 4 – 4%, grade 3 – 23%. BOPP – not published. MOPP – 34% previously untreated; BOPP – 43% previously untreated.	Nitrogen mustard (12 mg/m ² /course) Equivalent to BCNU (80 mg/m ² /course)
2	BCNU, Procarbazine [27]	Randomized	Hodgkin lymphoma MOPP (N = 104; median age, 38 years; M:F = 2.13:1.00) BOPP (N = 103; median age, 33 years; M:F = 1.56:1.00) BOP (N = 107; median age, 37 years; M:F = 1.56:1.00) OPP (N = 112; median age, 32 years; M:F = 2.13:1.00)	BOP <ul style="list-style-type: none"> • B (BCNU) - 80 mg/m² • O (Oncovin, vincristine) - 2.8 mg/m² • P (prednisone) - 560 mg/m² OPP <ul style="list-style-type: none"> • O (Oncovin, vincristine) - 2.8 mg/m² • P (prednisone) - 560 mg/m² • P (procarbazine) - 50 mg, day 1, 100 mg, day 2, 100 mg/m², days 3 – 13 	“Approximately the same degree of hematological toxicity” OPP – 34% previously untreated; BOP – 33% previously untreated.	BCNU (80 mg/m ² /course) Equivalent to Procarbazine (1200 mg/m ² + 150 mg/course)

Study	Drug(s) of interest	Study Design	Study Description	Drug doses per course	Toxicity	Alkylating agent dose evaluated
3	CCNU, Nitrogen mustard [25]	Randomized	Hodgkin lymphoma MOPP (N = 138; median age, 30 years; M:F = 1.44:1.00) MVPP (N = 124; median age, 36 years; M:F = 2.03:1.00) COPP (N = 133; median age, 36 years; M:F = 1.33:1.00) CVPP (N = 137; median age, 27 years; M:F = 1.78:1.00)	COPP <ul style="list-style-type: none"> C (CCNU) - 75 mg/m² O (Oncovin, vincristine) - 2.8 mg/m² P (procarbazine) - 1400 mg/m² P (prednisone) - 560 mg/m² MOPP <ul style="list-style-type: none"> M (Mustargen, nitrogen mustard) - 12 mg/m² O (Oncovin, vincristine) - 2.8 mg/m² P (procarbazine) - 1400 mg/m² P (prednisone) - 560 mg/m² 	MOPP – 15% grade 3 and 7 % grade 4 leukopenia in previously untreated patients; COPP – 21% grade 3 and 3 % grade 4 leukopenia in previously untreated patients	Nitrogen mustard (12 mg/m ² /course) Equivalent to CCNU (75 mg/m ² /course)
4	Chlorambucil [29]	Single arm study	Hodgkin lymphoma ChlVPP (N = 70; median age, 27 years; M:F = 2.04:1.00)	ChlVPP <ul style="list-style-type: none"> Chl (chlorambucil) - 84 mg/m² V (vinblastine) - 12 mg/m² P (procarbazine) - 1400 mg/m² P (prednisolone) - mg/m² 560 	Delay of initiation of next course for WBC < 3,000/mm ³ or platelets < 80,000/mm ³ in 15 patients (~ 21% of patients) (22 courses)	Chlorambucil (84 mg/m ² /course)
5	Chlorambucil [32]	Single arm study	Hodgkin lymphoma ChlVPP (N = 24) (previously untreated (N = 12) - median age, 31 years; M:F = 1.00:2.00; previously treated (N = 12) - median age - 28 years; M:F = 1.00:1.00)	ChlVPP <ul style="list-style-type: none"> Chl (chlorambucil) - 84 mg/m² V (vinblastine) - 12 mg/m² P (procarbazine) - 1400 mg/m² P (prednisolone) - 560 mg/m² 	Grade 4 leukopenia and/or thrombocytopenia – 29%	Chlorambucil (84 mg/m ² /course)

Study	Drug(s) of interest	Study Design	Study Description	Drug doses per course	Toxicity	Alkylating agent dose evaluated
6	Vinblastine [25]	Randomized	Hodgkin lymphoma MOPP (N = 138; median age, 30 years; M:F = 1.44:1.00) MVPP (N = 124; median age, 36 years; M:F = 2.03:1.00) COPP (N = 133; median age, 36 years; M:F = 1.33:1.00) CVPP (N = 137; median age, 27 years; M:F = 1.78:1.00)	MVPP <ul style="list-style-type: none"> • M (Mustargen, nitrogen mustard) - 12 mg/m² • V (vinblastine) - 8 mg/m² • P (procarbazine) - 1400 mg/m² • P (prednisone) - 560 mg/m² 	MVPP - 25% grade 3 and 3 % grade 4 leukopenia in previously untreated patients	
7	Chlorambucil, Nitrogen mustard [34]	Randomized	Hodgkin lymphoma MOPP (N = 153; median age, not reported; M:F = 2.06:1.00) LOPP (N = 136; median age, not reported; M:F = 2.68:1.00)	MOPP <ul style="list-style-type: none"> • M (Mustargen, nitrogen mustard) - 12 mg/m² • O (Oncovin, vincristine) - 2.8 mg/m² • P (procarbazine) - 1000 mg/m² • P (prednisone) - 350 mg/m² LOPP <ul style="list-style-type: none"> • L (Leukeran, chlorambucil) - 100 mg • O (Oncovin, vincristine) - 2.8 mg/m² • P (procarbazine) - 1000 mg/m² • P (prednisone) - 350 mg/m² 	WHO grade 2 hematologic - MOPP - 52% LOPP - 13% No grade 3 or 4 with either regimen	
8	Chlorambucil, Nitrogen mustard [33]	Randomized	Hodgkin lymphoma MOPP (N = 43; mean age, 33 years; M:F = 2.07:1.00) LOPP (N = 40; mean age, 35 years; M:F = 1.67:1.00)	MOPP <ul style="list-style-type: none"> • M (Mustargen, nitrogen mustard) - 12 mg/m² • O (Oncovin, vincristine) - 2.8 mg/m² • P (procarbazine) - 1400 mg/m² • P (prednisone) - 840 mg/m² LOPP 	Grades 3 - 4 leukopenia - MOPP - 23% LOPP 12% Grades 3 - 4 thrombocytopenia - MOPP - 22% LOPP - 1%	

Study	Drug(s) of interest	Study Design	Study Description	Drug doses per course	Toxicity	Alkylating agent dose evaluated
				<ul style="list-style-type: none"> L (Leukeran, chlorambucil) - 60 mg/m² O (Oncovin, vincristine) - 2.8 mg/m², P (procarbazine) - 1000 mg/m² P (prednisone) - 600 mg/m² 		
9	Nitrogen mustard [35]	Single arm study	Hodgkin lymphoma MOPP (N = 43; mean age, 31 years; M:F – 1.15:1.00)	MOPP <ul style="list-style-type: none"> M (Mustargen, nitrogen mustard) - 12 mg/m², O (Oncovin, vincristine) - 2.8 mg/m², P (procarbazine) - 1400 mg/m² P (prednisone) - 560 mg/m² 	Grade 2 to 4 leukopenia – 37%	Nitrogen mustard – 12 mg/m ² /course
10	Cyclophosphamide [28]	Single arm study	Hodgkin lymphoma COPP (N = 138; median age, 38 years; M:F – 1.56:1.00)	COPP <ul style="list-style-type: none"> C (cyclophosphamide) - 1200 mg/m² O (Oncovin, vincristine) - 2.8 mg/m² P (procarbazine) - 1400 mg/m² P (prednisone) - 560 mg/m² 	Grade 1 to 4 leukopenia – 39.5%	Cyclophosphamide – 1200 mg/m ² /course
11	Nitrogen mustard, melphalan [36]	Randomized	Hodgkin lymphoma MOP(P) (N = 52; mean age, 29.9 years; M:F – 2.13:1.00) PAVe (N = 53; mean age, 26.5 years; M:F – 1.36:1.00)	MOPP <ul style="list-style-type: none"> M (Mustargen, nitrogen mustard) - 12 mg/m² O (Oncovin, vincristine) - 2.8 mg/m² P (procarbazine) - 1400 mg/m² P (prednisone) – 560 mg/m² PAVe	Mean lowest recorded WBC - MOPP – 2,900/mm ³ PAVe – 2,600/mm ³	Nitrogen mustard – 12 mg/m ² /course Equivalent to Melphalan – 30 mg/m ² /course

Study	Drug(s) of interest	Study Design	Study Description	Drug doses per course	Toxicity	Alkylating agent dose evaluated
				<ul style="list-style-type: none"> P (procarbazine) - 1400 mg/m² A (Alkeran, chlorambucil) - 30 mg/m² Vc (Velban, vinblastine) - 12 mg/m² 		
12	Melphalan BCNU CCNU[39]	Randomized	Multiple myeloma Melphalan (N = 100; median age, 62 years; M:F = 1.38:1.00) BCNU (N = 124; median age, 62 years; M:F = 1.38:1.00) CCNU (N = 135; median age, 64 years; M:F = 1.13:1.00)	Melphalan - 1.05 mg/kg (Induction) + 5.60 mg/kg (Maintenance) BCNU - 600 mg/m ² CCNU - 400 mg/m ²	Grade 4 leukopenia - Melphalan - 5%, BCNU - 3%, CCNU - 4% Percentage of the planned cumulative drug dose actually administered in each of the three arms was not reported	
13	Melphalan Cyclophosphamide [38]	Randomized	Multiple myeloma Melphalan (N = 71; mean age, not reported; all males) Cyclophosphamide (N = 63; mean age, not reported; all males)	Melphalan - 0.1 mg/kg/day Cyclophosphamide - 4 mg/kg/day	Grade 3 - 4 leukopenia - Melphalan - 43.7% Cyclophosphamide - 47.6%, Platelet count < 60,000/ml ³ - Melphalan - 43.7%, Cyclophosphamide - 28.6%	Melphalan - 0.1 mg/kg/day Equivalent to Cyclophosphamide - 4 mg/kg/day
14	Cyclophosphamide Ifosfamide [40]	Randomized	Rhabdomyosarcoma VAC (N = 235; mean age, not reported; M:F = 1.37:1.00) VAI (N = 222; mean age, not reported; M:F = 1.31:1.00)	VAC <ul style="list-style-type: none"> V (vincristine) - 9.0 mg/m² A (actinomycin D) - 0.15 mg/kg C (cyclophosphamide) - 4.4 g/m² VAI <ul style="list-style-type: none"> V (vincristine) - 9.0 mg/m², A (actinomycin D) - 0.15 mg/kg I (ifosfamide) - 18 g/m² 	No difference in % Grade 3, 4 or 5 or grades 3 to 5 combined toxicity	Cyclophosphamide - 4.4 g/m ² /course Equivalent to Ifosfamide - 18.0 g/m ² /course
15	Busulfan Cyclophosphamide [51]	Randomized	Chronic myelocytic leukemia	Busulfan - 0.1 mg/kg/day Cyclophosphamide - 2 mg/kg/day	"Dose adjustments necessary in both groups to...prevent	Based on the mean doses required to achieve a partial remission, Busulfan 136 mg/m ²

Study	Drug(s) of interest	Study Design	Study Description	Drug doses per course	Toxicity	Alkylating agent dose evaluated
16	Busulfan, Cyclophosphamide [41, 42, 52]	Randomized	Busulfan (N = 20; mean age, 40.2 years; all males) Cyclophosphamide (N = 21; mean age, 47.2 years; all males)	Busulfan - Induction (10 days) - 4 mg/day, maintenance - 1.5 mg/day (two years) Cyclophosphamide - Induction (10 days) - 200 mg/day, maintenance - 75 mg/day (two years)	excessive medication depression." The mean cyclophosphamide dose was 76 mg/kg (range, 30 to 252 mg/kg) compared to 8.6 mg/kg (range, 4.2 to 14.8 mg/kg) for busulfan 35.	Equivalent to Cyclophosphamide 1200 mg/m ²
17	Thio-TEPA, Nitrogen mustard [43]	Randomized	Lung carcinoma Busulfan (N = 243; mean age, not reported; M:F = 12.50:1.00) Cyclophosphamide (N = 234; mean age, not reported; M:F = 10.70:1.00) Placebo (N = 249; mean age, not reported; M:F = 12.83:1.00)	Thio-TEPA - 0.8 mg/kg (Induction) + 0.2 mg/kg/week (Maintenance) Nitrogen mustard - 0.4 mg/kg (Induction) + 0.1 mg/kg/week (maintenance)/course	Grade 2 to 4 leukopenia at any time during treatment - Busulfan - 23%, Cyclophosphamide - 16%. The differences in frequency of grades 2 to 4 leukopenia following the induction and the percentage of planned dose administered during maintenance were not reported	Thio-TEPA - 0.2 mg/kg Equivalent to Nitrogen mustard - 0.1 mg/kg

Table II

Alkylating agent dose equivalents derived from published studies

Study	Cyclophosphamide	Ifosfamide	Procarbazine	Chlorambucil	BCNU	CCNU	Melphalan	Thio-TEPA	Nitrogen mustard	Busulfan
1					80 mg/m ²				12 mg/m ²	
2			1200 mg/m ² + 150 mg		80 mg/m ²					
3						75 mg/m ²			12 mg/m ²	
5				84 mg/m ²						
6									12 mg/m ²	
9									12 mg/m ²	
10	1200 mg/m ²									
11							30 mg/m ²		12 mg/m ²	
13	120 mg/m ²						3 mg/m ²			
14	4400 mg/m ²	18000 mg/m ²								258 mg/m ²
15	2280 mg/m ²									
17								6 mg/m ²	3 mg/m ²	
Equivalent dose	100 mg/m ²	409 mg/m ²	117 mg/m ²	7 mg/m ²	6.7 mg/m ²	6.3 mg/m ²	2.5 mg/m ²	2 mg/m ²	1 mg/m ²	11.3 mg/m ²

Table III
Hazard Ratio of Pregnancy among Partners of Male Childhood Cancer Survivors Using CED or AAD

Characteristic	CED			AAD		
	HR	95% CI	p-value	HR	95% CI	p-value
Age at Diagnosis (years)						
0 to 4	1.82	1.33 to 2.49	< 0.001	1.80	1.31 to 2.47	<0.001
5 to 9	1.19	0.92 to 1.54	0.192	1.16	0.89 to 1.50	0.27
10 to 14	0.97	0.78 to 1.21	0.806	0.95	0.76 to 1.18	0.65
15 to 20	1.00			1.00		
Education						
No High school/GED	1.00			1.00		
High school/GED	0.74	0.55 to 1.01	0.056	0.75	0.55 to 1.02	0.069
Some college	0.68	0.52 to 0.90	0.007	0.69	0.52 to 0.91	0.01
Bachelor or higher	0.51	0.39 to 0.67	< 0.001	0.53	0.40 to 0.71	<0.001
Race/Ethnicity						
White	1.00			1.00		
Black	1.87	1.27 to 2.76	0.001	1.91	1.29 to 2.84	0.001
Hispanic	1.09	0.51 to 2.33	0.819	1.13	0.53 to 2.41	0.75
Other	1.30	0.99 to 1.71	0.063	1.35	1.02 to 1.78	0.035
Marital Status						
Never married	1.00			1.00		
Currently married	9.48	7.18 to 12.52	< 0.001	9.64	7.23 to 12.85	<0.001
Formerly married	6.18	4.31 to 8.87	< 0.001	6.36	4.40 to 9.20	<0.001
Hypothalamic/pituitary Radiation Dose						
None	1.00			1.00		
> 0 to 4000 cGy	0.58	0.14 to 2.40	0.449	0.52	0.13 to 2.16	0.37
> 4000 cGy	0.32	0.07 to 1.42	0.133	0.29	0.06 to 1.28	0.10
Testicular Radiation Dose						
None	1.00			1.00		
> 0 to 750 cGy	1.49	0.36 to 6.20	0.587	1.62	0.39 to 6.71	0.51

Characteristic	CED			AAD		
	HR	95% CI	p-value	HR	95% CI	p-value
> 750 cGy	0.12	0.02 to 0.61	0.011	0.12	0.02 to 0.64	0.012
CED (mg/m²)						
None	1.00					
0 to < 4,000	0.91	0.67 to 1.24	0.564			
4,000 to < 8,000	0.72	0.55 to 0.95	0.019			
8,000 to < 12,000	0.49	0.36 to 0.68	< 0.001			
12,000 to < 16,000	0.37	0.24 to 0.57	< 0.001			
16,000 to < 20,000	0.53	0.34 to 0.82	0.004			
20,000	0.17	0.10 to 0.29	< 0.001			
Summed AAD						
0				1.00		
1				0.95	0.68 to 1.33	0.77
2				0.67	0.51 to 0.88	0.004
3				0.48	0.36 to 0.65	< 0.001
4				0.34	0.22 to 0.52	< 0.001
5				0.38	0.22 to 0.66	< 0.001
6 to 11				0.16	0.08 to 0.32	< 0.001
Cytosine Arabinoside						
No	1.00			1.00		
Yes	1.82	1.37 to 2.43	< 0.001	1.80	1.35 to 2.40	< 0.001
Actinomycin D						
No	1.00			1.00		
Yes	1.05	0.83 to 1.34	0.667	0.97	0.76 to 1.23	0.78
Daunorubicin						
No	1.00			1.00		
Yes	1.03	0.74 to 1.42	0.864	1.10	0.79 to 1.52	0.58
Vinblastine						
No	1.00			1.00		

Characteristic	CED			AAD		
	HR	95% CI	p-value	HR	95% CI	p-value
Yes	1.00	0.60 to 1.67	0.988	1.11	0.59 to 2.08	0.75
Vincristine						
No	1.00			1.00		
Yes	1.04	0.85 to 1.28	0.690	1.07	(0.87 to 1.32)	0.53
VM-26						
No	1.00			1.00		
Yes	1.17	0.70 to 1.97	0.545	1.05	(0.62 to 1.79)	0.84

HR – Hazard Ratio; CI – Confidence Interval; CED – Cyclophosphamide Equivalent Dose; AAD – Alkylating Agent Dose score. All factors displaying estimates for a specific column are included together in that multivariate model. HR controlled for age at diagnosis, education, race/ethnicity and marital status. Values shown in **bold** font are statistically significant.

Table IV
Rate Ratios for Non-Surgical Premature Menopause: Multiple Poisson Regression Model

Variable	CED			AAD		
	RR	95% CI	p-value	RR	95% CI	p-value
Age	1.14	1.09 to 1.20	< 0.001	1.13	1.07 to 1.19	< 0.001
Minimum ovarian dose						
Other cancers						
None	1.00			1.00		
1 to 99 cGy	2.96	0.92 to 9.50	0.069	4.25	1.18 to 15.26	0.027
100 cGy	11.68	3.59 to 38.04	< 0.001	16.77	4.55 to 61.88	< 0.001
Hodgkin lymphoma						
None	13.86	4.04 to 47.57	< 0.001	9.88	1.65 to 59.24	0.012
1 to 99 cGy	10.04	3.40 to 29.65	< 0.001	12.73	3.55 to 45.57	< 0.001
100 cGy	10.76	3.32 to 34.91	< 0.001	10.73	2.70 to 42.64	< 0.001
CED (mg/m ²)						
0	1.00					
> 0 to < 4,000	0.56	0.07 to 4.27	0.578			
4,000 to < 8,000	2.74	1.13 to 6.61	0.025			
8,000	4.19	2.18 to 8.08	< 0.001			
AAD tertile						
0				1.00		
1 to 2				2.09	0.97 to 4.51	0.060
3				4.99	2.53 to 9.84	< 0.001

CED – Cyclophosphamide Equivalent Dose; AAD – Alkylating Agent Dose score; RR – Rate Ratio; CI – Confidence Interval; Values shown in **bold** font are statistically significant.

Table V
Odds Ratios for Dental Outcomes Among Childhood Cancer Survivors: Multivariable Logistic Regression Models

	CED			AAD		
	OR	95% CI	p-value	OR	95% CI	p-value
Abnormal Roots						
CED (mg/m²)						
0	1.0					
> 0 to < 4,000	1.2	0.9 to 1.8	0.245			
4,000 to < 8,000	1.3	0.9 to 1.9	0.101			
8,000	2.0	1.5 to 2.6	< 0.001			
AAD fertility						
0				1.0		
1				1.3	1.0 to 1.7	0.071
2				1.9	1.4 to 2.5	< 0.001
3				2.2	1.5 to 3.1	< 0.001
RT dose (cGy)						
0	1.0			1.0		
> 0 to < 2000	2.3	1.7 to 2.9	< 0.001	2.3	1.7 to 2.9	< 0.001
2000	16.0	10.0 to 25.8	< 0.001	16.0	9.9 to 25.6	< 0.001
Antimetabolites						
No	1.0			1.0		
Yes	1.2	0.9 to 1.6	0.296	1.2	0.9 to 1.6	0.238
Steroids						
No	1.0			1.0		
Yes	0.8	0.6 to 1.2	0.285	0.8	0.6 to 1.1	0.234
Vincristine						
No	1.0			1.0		
Yes	1.1	0.8 to 1.5	0.592	1.1	0.8 to 1.5	0.569
Hypodontia						
CED (mg/m²)						

	CED			AAD		
	Abnormal Roots					
	OR	95% CI	p-value	OR	95% CI	p-value
0	1.0					
> 0 to < 4,000	1.7	1.3 to 2.3	0.001			
4,000 to < 8,000	2.2	1.7 to 2.9	< 0.001			
8,000	2.4	1.9 to 2.9	< 0.001			
AAD fertile						
0				1.0		
1				1.8	1.4 to 2.2	< 0.001
2				2.4	1.9 to 3.1	< 0.001
3				2.8	2.1 to 3.7	< 0.001
RT dose (cGy)						
0	1.0			1.0		
> 0 to < 2000	1.2	1.0 to 1.5	0.038	1.2	1.0 to 1.5	0.048
2000	3.5	2.2 to 5.6	< 0.001	3.4	2.1 to 5.4	< 0.001
Antimetabolites						
No	1.0			1.0		
Yes	0.8	0.6 to 1.0	0.110	0.9	0.7 to 1.1	0.247
Steroids						
No	1.0			1.0		
Yes	1.0	0.8 to 1.3	0.918	0.9	0.7 to 1.2	0.678
Vincristine						
No	1.0			1.0		
Yes	1.0	0.8 to 1.2	0.746	0.9	0.7 to 1.2	0.653
	Microdontia					
CED (mg/m ²)						
0	1.0					
> 0 to < 4,000	1.5	1.1 to 2.0	0.008			
4,000 to < 8,000	1.7	1.3 to 2.3	< 0.001			

	CED			AAD		
	Abnormal Roots					
	OR	95% CI	p-value	OR	95% CI	p-value
8,000	2.1	1.7 to 2.6	< 0.001			
AAD tertile						
0				1.0		
1				1.6	1.3 to 2.0	< 0.001
2				2.1	1.7 to 2.7	< 0.001
3				2.1	1.5 to 2.7	< 0.001
RT dose (cGy)						
0	1.0			1.0		
> 0 to < 2000	1.3	1.1 to 1.6	0.004	1.3	1.1 to 1.6	0.004
2000	3.1	1.9 to 4.9	< 0.001	3.1	1.9 to 4.9	< 0.001
Antimetabolites						
No	1.0			1.0		
Yes	1.0	0.8 to 1.3	0.856	1.0	0.8 to 1.3	0.911
Steroids						
No	1.0			1.0		
Yes	0.6	0.5 to 0.8	0.001	0.6	0.5 to 0.8	0.001
Vincristine						
No	1.0			1.0		
Yes	1.2	0.9 to 1.5	0.135	1.2	1.0 to 1.5	0.124
	Enamel					
CED (mg/m ²)						
0	1.0					
> 0 to < 4,000	1.3	1.0 to 1.7	0.045			
4,000 to < 8,000	1.4	1.1 to 1.8	0.007			
8,000	1.4	1.1 to 1.7	0.001			
AAD tertile						
0				1.0		

	CED			AAD		
	Abnormal Roots					
	OR	95% CI	p-value	OR	95% CI	p-value
1				1.3	1.1 to 1.6	0.007
2				1.3	1.0 to 1.6	0.022
3				1.6	1.2 to 2.1	< 0.001
RT dose (cGy)						
0	1.0			1.0		
> 0 to < 2000	1.2	1.0 to 1.4	0.027	1.2	1.0 to 1.4	0.026
2000	3.5	2.2 to 5.4	< 0.001	3.4	2.2 to 5.3	< 0.001
Antimetabolites						
No	1.0			1.0		
Yes	1.0	0.8 to 1.2	0.847	1.0	0.8 to 1.3	0.873
Steroids						
No	1.0			1.0		
Yes	1.1	0.8 to 1.3	0.620	1.0	0.8 to 1.3	0.854
Vincristine						
No	1.0			1.0		
Yes	1.1	0.9 to 1.4	0.340	1.1	0.9 to 1.4	0.348
	> Six Cavities					
CED (mg/m ²)						
0	1.0					
> 0 to < 4,000	1.0	0.8 to 1.2	0.740			
4,000 to < 8,000	1.0	0.8 to 1.2	0.936			
8,000	1.4	1.2 to 1.5	< 0.001			
AAD fertile						
0				1.0		
1				1.0	0.9 to 1.1	0.846
2				1.4	1.2 to 1.6	< 0.001
3				1.3	1.1 to 1.6	0.005

	CED				AAD			
	Abnormal Roots							
	OR	95% CI	p-value	OR	95% CI	p-value		
RT dose (cGy)								
0	1.0			1.0				
> 0 to < 2000	1.1	1.0 to 1.3	0.013	1.1	1.0 to 1.3	0.015		
2000	2.0	1.3 to 3.1	0.001	2.0	1.3 to 3.0	0.001		
Antimetabolites								
No	1.0			1.0				
Yes	0.9	0.8 to 1.1	0.407	0.9	0.8 to 1.1	0.376		
Steroids								
No	1.0			1.0				
Yes	1.1	1.0 to 1.3	0.139	1.1	1.0 to 1.3	0.116		
Vincristine								
No	1.0			1.0				
Yes	0.9	0.8 to 1.1	0.252	0.9	0.8 to 1.1	0.256		

OR – Odds Ratio; CI –Confidence Interval; CED – Cyclophosphamide Equivalent Dose; AAD – Alkylating Agent Dose score. Each alkylating agent variable (AAD or CED) is included in a separate model adjusted for age at follow-up, sex, race/ethnicity, education, household income, health insurance, vincristine, RT, antimetabolites and steroids. Values shown in **bold** font are statistically significant.