LATE EFFECTS OF TREATMENT

FOR CANCER DURING CHILDHOOD AND ADOLESCENCE

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Survival after the diagnosis of cancer in children and adolescents has become the rule, rather than the exception. As a result, there is an increasing population of young and middle aged adults who, having been cancer free for many years, have concerns regarding the effects of their therapy on their longevity, fertility and offspring. This review will discuss the effects of treatment responsible for the two most frequent causes of premature mortality in disease-free survivors – cardiac disease and second malignant neoplasms, and the effects of treatment on fertility and pregnancy outcome.

CARDIAC DAMAGE

Radiation Damage

The heart may be damaged by both therapeutic irradiation and by chemotherapeutic agents. Radiation-related damage to the heart was examined in a series of patients with several diagnoses, including Hodgkin's disease and carcinoma of the breast by investigators at Stanford University in 1967 (1,2). Several types of damage were recognized, including pericardial, myocardial and vascular.

The frequency of radiation related cardiac damage is related to the technique of irradiation employed. The original mantle field technique employed equally weighted anterior and posterior fields, high dose-rate pulmonary irradiation, and no subcarinal block. Pericarditis was diagnosed in 17.1% (43/251) of patients who received this treatment. The use of a "thin lung block" to decrease the dose rate to the lungs, and the addition of a subcarinal block to decrease the amount of pericardium treated to the full

dose decreased the frequency of pericarditis to 2.5% (2/79) (3,4) (Table 1). The frequency of pericarditis was 3.2% (3/93) in a series of adult patients treated using the original mantle field technique, with the treatment delivered over a longer period of time using smaller radiation fractions (5), and was 0% - 2.5% among pediatric patients treated using an equally weighted anterior-posterior mantle technique (6,7,8). The frequency of radiation related pericarditis was correlated with the total pericardial radiation dose (3).

Patients who were treated for Hodgkin's disease with anterior only or anteriorly weighted field arrangements had a higher frequency of pericarditis. Twenty-two of 87 such patients (25.3%) developed radiographic evidence of a pericardial effusion. Six the patients (6.9%) developed cardiac tamponade not due to a malignant effusion (9). Chronic pericarditis was diagnosed in 11.1% (9/81) of patients treated for Hodgkin's disease with radiation therapy that included the mediastinum using an anteriorly weighted mantle treatment technique. Seven of these patients (77.8%) had previous documentation of a pericardial effusion, and eight presented with some degree of exertional dyspnea previously attributed to other factors. Chronic pericardial disease was diagnosed 53-124 months following irradiation, suggesting that prolonged follow-up of such patients is necessary to identify this complication (10).

Byhardt et al confirmed the increased risk of pericardial damage associated with the use of an anteriorly weighted mantle field. Twenty-four of 83 patients (28.9%) who received this treatment developed radiographic evidence of a pericardial effusion a mean of 150 days after the completion of thoracic irradiation. The frequency of pericarditis was correlated with the size of the mediastinal mass, but not with the

radiation dose, suggesting that, within the dosage range examined, the amount of pericardium included within the radiation volume was the most critical variable (11).

Coltart et al identified severe constrictive pericarditis in four of 73 patients (5.5%) treated for Hodgkin's disease using only an anterior mediastinal field and a 16 meV linear accelerator (12).

Several groups of investigators reported the results of long-term evaluations of cardiac function following mantle irradiation. Applefeld et al diagnosed constrictive pericarditis in 32% (8/25), occult constrictive pericarditis in 32% (8/25), occlusive coronary artery disease in 12% (3/25) and cardiomyopathy in 4% (1/25) of patients evaluated 37-144 months after the completion of mantle irradiation administered using an anteriorly weighted technique (13).

Gomez et al. reported a statistically significant decrease in transverse cardiac diameter among patients who had received mediastinal irradiation for Hodgkin's disease compared to patients who had not received mediastinal irradiation. The first pass left ventricular ejection fraction measured using a radionuclide technique was less than 43% in 12 of 55 patients (21.8%) following treatment using an equally weighted anterior-posterior technique and a total treatment dose of 3600 cGy. A subcarinal shield was not routinely employed (14). Morgan et al. evaluated cardiac function in 25 adult patients 5 - 16 years after completion of mediastinal irradiation administered using an equally weighted anterior-posterior technique, and a total treatment dose of 4000 cGy. The cardiac apex was shielded after 1500 cGy, and a subcarinal cardiac shield was placed after 3000 cGy. The radionuclide ejection fraction was less than 43% in only one of 23 patients (4.4%). The patient with the low ejection fraction was clinically hypothyroid at

the time of cardiac evaluation. Right ventricular enlargement, interpreted as a direct effect of irradiation on the right ventricular myocardium rather than an effect of pulmonary complications of irradiation, was identified in six of 25 (24%) patients (15). No patient in either of these two series had symptoms of congestive heart failure or constrictive pericarditis. The difference in the frequency of low ejection fractions reported in these two studies may be related to the differences in the treatment technique employed, or to differences in the performance and interpretation of the radionuclide ventriculography.

Cardiac function has been evaluated in three series of long-term survivors treated during childhood or adolescence for Hodgkin's disease using megavoltage technique. In one series, all 28 patients treated with equally weighted anterior and posterior treatment technique had a normal cardiothoracic ratio and none had a decreased left ventricular ejection fraction, determined using echocardiographic techniques. Pericardial thickening was demonstrated on echocardiograms from 12 of the 28 patients (42.9%). Thickening was more frequent among those patients observed for 72 or more months (47.1%; 8/17) than among those with shorter periods of follow-up (36.4%; 4/11) (16). In another study, one of 14 patients studied 1 – 48 months after completion of chemotherapy had an abnormal resting radionuclide ejection fraction (17); and in the third, the mean left ventricular ejection fraction and mean peak (left ventricular) filling rate were normal for a group of 12 patients who were less than 20 years of age when irradiated (18,19).

Hancock and his colleagues evaluated cardiac disease in a series of 635 patients who were less than 21 years of age at diagnosis, and were treated at Stanford

University Medical Center (SUMC) for Hodgkin disease using various megavoltage techniques. The relative risk (RR) of death due to any cardiac disease was 29.6 (95% confidence interval (CI) 16.0, 49.3). The RR was 28.1 (95% CI 12.3, 55.5) for those treated with radiation therapy only, and was 37.1 (95% CI 13.6, 82.5) for those treated with radiation therapy and chemotherapy. Seven of the 12 deaths were due to acute myocardial infarction, three from valvular or congenital heart disease and two from pericarditis or pancarditis. Twenty-six of the 635 patients developed new cardiac murmurs, an unknown fraction of which was felt probably to be benign flow murmurs (20). Radiation-related valvular disease is being recognized with increasing frequency, with the aortic valve most frequently involved (21,22). Symptomatic disease may not appear until 7 – 39 years after mediastinal irradiation (22).

Chemotherapy Damage

The anthracycline antibiotics, daunorubicin and doxorubicin, cause a dose-related cardiomyopathy (Table 2). Early studies suggested that cardiomyopathy was uncommon in adults who had received cumulative doxorubicin doses that did not exceed 550 - 600 mg/square meter (23,24). The frequency of cardiomyopathy was reduced by modifying the schedule of anthracycline administration. Congestive heart failure was diagnosed in 5.4% (8/149) of patients who received doxorubicin using a weekly, low dose schedule to a cumulative dose of more than 600 mg/square meter. Sixty-four of these patients received cumulative doses of doxorubicin that exceeded 1000 mg/square meter (25,26).

Torti et al investigated the effect of treatment schedule on the severity of doxorubicin cardiomyopathy using endomyocardial biopsy specimens. Less severe

injury was associated with a lower cumulative doxorubicin dose and administration using a weekly schedule (27). Legha et al. demonstrated that the frequency of severe morphologic changes in endomyocardial biopsy specimens was lower in patients who received a continuous infusion of doxorubicin, compared to patients who received the drug using a high-dose rate, every third week administration schedule (28).

Von Hoff et al. analyzed the frequency of congestive heart failure in 3941 patients whose treatment included doxorubicin. The cumulative risk of congestive heart failure was correlated with the age of the patient, the total anthracycline dose administered, and the schedule of drug administration employed. Older patients who received the drug every third week had the greatest risk of developing congestive heart failure at a given cumulative drug dose, compared either to younger patients, or those treated with a weekly schedule. Neither a previous history of mediastinal irradiation, nor the concurrent administration of other potentially cardiotoxic agents, such as cyclophosphamide, was shown to influence the risk of developing congestive heart failure, once the effects of age, schedule and cumulative dose were considered (29).

The study by Von Hoff et al. suggested that children had a decreased risk of cardiomyopathy compared to adults at any given cumulative doxorubicin dose (29). Other data suggested that the risk of cardiomyopathy was increased in children (30,31).

Recent studies confirmed the strong relationship between cumulative anthracycline dose and the frequency of cardiac function abnormalities in anthracycline treated children and adolescents. Silber et al reported that the odds ratio for having a cardiac test abnormality was 5.2 for cumulative anthracycline doses of 400 mg/M^2 compared to 100 mg/M^2 (32). Steinherz et al reported poor cardiac functioning at late

testing in 11% (9/79) of patients treated with less than 400 mg/M^2, compared to 23% (22/96) of those treated with 400 – 599 mg/M^2, 47% of those treated with 600 – 799 mg/M^2, and 100% of seven patients treated with more than 800 mg/M^2 (33). Bu'Lock et al reported a shortening fraction of < 35% in 48% (11/23) of patients who received $\leq$ 100 mg/M^2 of anthracycline, compared to 40% (19/48) who received 101 - 200 mg/M^2, 46% (22/48) of those who received 201 - 300 mg/M^2, 73% (36/49) of those who received 301 - 400 mg/M^2, 83% (38/46) of those who received 401 - 500 mg/M^2, and 83% (10/12) of those who received $\geq$ 500 mg/M^2 (34). Green and his colleagues reported that the RR of congestive heart failure was 3.3 for every 100 mg/M^2 of anthracycline (35). Johnson et al did not identify a relationship between cumulative anthracycline dose and change in shortening fraction in a study of 28 patients (36), and others did not evaluate the relationship between cumulative anthracycline dose and abnormalities of left ventricular function (37,38,39,40).

Another risk factor for congestive heart failure is female gender. This was associated with a four-fold elevation in risk of congestive heart failure in the National Wilms Tumor Study Group cohort reported by Green et al (35). This finding is consistent with earlier reports of an increased risk of impaired cardiac function in anthracycline treated female survivors of acute lymphoblastic leukemia or osteosarcoma (41). Silber et al. reported a RR of 3.2 for a cardiac test abnormality in females compared to males (32), and Krischer et al reported a RR of 1.9 for the occurrence of clinical cardiotoxicity (congestive heart failure, sudden death, or abnormal measurements of cardiac function) in anthracycline exposed females compared to males (42). Others found no effect of gender on the risk of impaired cardiac function in anthracycline treated Wilms tumor survivors

(43), acute lymphoblastic leukemia survivors (44), or survivors with various diagnoses (34). Several studies did not evaluate the effect of gender on cardiac function (36,37,38,45).

Radiation therapy to a volume that included the left ventricle increased the RR of congestive heart failure. The increase was 1.6 for every 1000 cGy of thoracic irradiation and 1.8 for every 1000 cGy of left abdominal irradiation (35). Previous case reports suggested that there might be a relationship between mediastinal (46) or abdominal irradiation (47,48) and cardiac function after treatment with anthracyclines. Bu'Lock et al reported symptomatic cardiac disease in 23% (5/22) of patients who had received cardiac irradiation, compared to 3% (6/204) among the unirradiated patients (34). Steinherz et al reported that mediastinal irradiation, as a dichotomous variable and mediastinal radiation dose were both significant predictors in univariate analyses of late cardiac dysfunction in anthracycline treated patients. Mediastinal irradiation, as a dichotomous variable, remained significant, along with cumulative anthracycline dose and duration of follow-up, in a linear regression analysis (33). Sorensen et al were unable to demonstrate such a relationship in their analysis of cardiac function in anthracycline exposed Wilms tumor patients (43), and Krischer et al were unable to demonstrate an effect of radiation that involved the heart on the risk of cardiotoxicity (42).

Krischer et al reported that the RR of clinical cardiotoxicity was 2.81 among those patients treated with $\geq$ 50 mg/M^2/week (42). Ewer et al reported no difference in the percentage of children treated with 60 – 75 mg/M^2 who developed cardiac dysfunction whether the drug was given as a single dose (11.8%; 2/17) or as equal divided doses on three consecutive days (13.5%; 13/96) (49).

Anthracycline administration may impair the growth potential of the left ventricular myocardium. Continued somatic growth will eventually result in an inadequate left ventricular mass, with resulting excessive afterload and depressed function. Left ventricular function and/or afterload was abnormal in 65.4%(36/55) of patients evaluated 0 - 13 years (median 6.7 years) after completion of therapy that included doxorubicin for acute lymphoblastic leukemia (50).

The elapsed time from treatment with doxorubicin to the onset of congestive heart failure is variable. Lipshultz and his colleagues demonstrated that left ventricular function worsened during the first two years after completion of treatment with doxorubicin. Left ventricular function then improved without becoming normal 2 – 6 years after the completion of therapy. Left ventricular function then progressively deteriorated during the period 7 –14 years after the completion of therapy (51).

Several investigators attempted to prospectively identify patients with anthracycline cardiomyopathy using non-invasive tests of cardiac function. Studies conducted in adult (52) and pediatric (53) patient populations were not able to reliably correlate changes in serially obtained pre-ejection period/left ventricular ejection time (PEP/LVET) ratios or electrocardiograms with the development of congestive heart failure. Others reported that quantitative radionuclide angiocardiography might allow identification of patients whose anthracycline therapy should be discontinued (54, 55).

Serial endomyocardial biopsies obtained from patients receiving anthracycline therapy at Stanford University demonstrated that cardiomyopathic effects were present in biopsy samples from patients who had received only 45 mg/M^2 of doxorubicin. Significant histological changes were observed at cumulative doxorubicin doses that did

not cause an increase in the PEP/LVET ratio (56). Patients with one or more of the following risk factors were shown to benefit from careful prospective, non-invasive and invasive, monitoring of cardiac function: previous mediastinal irradiation, history of coronary, valvular or myocardial heart disease, long-standing history of hypertension (diastolic blood pressure of more than 100 mm Hg obtained at least five years prior to the initiation of doxorubicin), age more than 70 years and previous treatment with more than 550 mg/ M^2 of doxorubicin. Patients without these risk factors have a negligible risk of anthracycline related cardiomyopathy and do not benefit from serial non-invasive monitoring of cardiac function (57).

Goorin et al. reported that 80% (12/15) of children survived the acute episode of congestive heart failure due to doxorubicin cardiomyopathy. However, only 20% (3/15) of these patients were able to discontinue digoxin therapy. Six had persistent evidence of myocardial failure, four of whom required continued digoxin treatment (58). Lewis et al. reported that some children with anthracycline induced left ventricular dysfunction may have spontaneous recovery of function following cessation of anthracycline therapy (59).

Cyclophosphamide is administered in high doses (greater than 140 mg/kg) to patients being prepared for bone marrow transplantation. This form of therapy has been employed experimentally for the treatment of patients with recurrent or metastatic neoplasms, including acute lymphoblastic and myelogenous leukemia, chronic myelogenous leukemia, neuroblastoma and Ewing's sarcoma. Acute cardiac failure has been reported following the administration of cyclophosphamide using such doses. Pathological examination reveals that the left ventricle is thickened and intramyocardial

hemorrhage is identified (60, 61, 62). Electrocardiographic changes were reported after 16.7% (5/30) to 22.2% (4/18) of courses of high dose cyclophosphamide treatment (61, 63). The frequency of cardiotoxicity is related to the dose of cyclophosphamide administered. Goldberg et al. reported cardiotoxicity in 3% (1/32) of patients who received 1.55 grams/ M^2/day or less of cyclophosphamide, compared to 25% (13/52) of patients who received a daily dose of more than 1.55 grams/ M^2 (64).

REPRODUCTION

Treatment with radiation therapy or chemotherapy may have adverse effects on germ cell survival, fertility and health of offspring.

Germ Cell Survival

Radiation therapy and chemotherapy may adversely affect germ cell survival. Ovarian damage results in both sterilization and loss of hormone production because ovarian hormonal production is closely related to the presence of ova and maturation of the primary follicle. These functions are not as intimately related in the testis. As a result, men may have normal androgen production in the presence of azoospermia.

Ovarian Damage

The number of oocytes in the ovary reaches a peak of 6.8×10^6 at five months of gestation. At birth there are approximately 2×10^6 primordial follicles present. This number decreases to 0.7×10^6 by six months of age, and to 0.3×10^6 by seven years of age (65). The non-renewable nature of oocytes renders the ovary uniquely susceptible to damage by radiation therapy and chemotherapeutic agents.

All women who receive total body irradiation prior to bone marrow transplantation develop amenorrhea. Recovery of normal ovarian function occurred in only nine of 144 patients, and was highly correlated with age at irradiation of less than 25 years (66).

The frequency of ovarian failure following abdominal radiation therapy is related both the age of the woman at the time of irradiation and the radiation therapy dose received by the ovaries.

Whole abdomen irradiation produces severe ovarian damage. Seventy-one percent of women in one series failed to enter puberty, and 26% had premature menopause following whole abdominal radiation therapy doses of 2000 to 3000 cGy (67). Others reported similar results in women treated with whole abdomen irradiation (68) or craniospinal irradiation (69,70) during childhood.

The frequency of ovarian failure is correlated with the treatment volume. Ovarian failure occurred in none of 34 women who received abdominal irradiation to a volume that did not include both ovaries, 14% of 35 whose ovaries were at the edge of the abdominal treatment volume, and 68% of 25 whose ovaries were entirely within the treatment volume (71). These reports corroborated a study of ovarian histology that identified severe ovarian damage in children who received abdominal irradiation, with or without chemotherapy (72).

Ovarian failure is correlated, in addition, with the radiation therapy dose. Ovarian failure occurred in 80% of five women who received 125 to 249 roentgens, 69% of 35 women who received 250 to 374 roentgens, 87% of 26 women who received 375 to 499 roentgens, 94% of 36 women who received 500 to 624 roentgens, and 100% of 72

women treated with 625 to 749 roentgens to both ovaries. The frequency of ovarian failure was lower among women less than 40 years of age who received radiation therapy doses less than 624 roentgens (73). These data are similar to the estimate for the LD50 of 600 cGy for the oocyte (74).

Limiting the ovarian radiation dose may preserve ovarian function. This can be accomplished in selected patients using midline oophoropexy (75,76), lateral ovarian transposition (77) or heterotopic ovarian autotransplantation (78). With midline oophoropexy, the ovarian doses received from pelvic irradiation can be limited to 220 to 550 cGy when the treatment dose is 4400 cGy (75), and in women who are less than 25 years of age at the time of treatment, ovarian failure is infrequent (Table 3) (75,79,80). One of these procedures should be considered prior to irradiation of any female child or adolescent who will receive pelvic irradiation.

Ovarian function was evaluated in women following treatment with combination chemotherapy (Table 4) (81,82,83,84). These studies, performed following treatment with the combination of nitrogen mustard, vincristine, procarbazine and prednisone (MOPP), the combination of nitrogen mustard, vinblastine, procarbazine and prednisone (MVPP) or the combination of chlorambucil, vinblastine, procarbazine and prednisone (ChlVPP), demonstrated the sensitivity of the older patient to the gonadal toxicity of such therapy (Table 5) (85,86,87,88), whether three or six cycles were administered (Table 6) (89). Younger women had a lower frequency of amenorrhea following treatment with one of these combinations.

Ovarian function was evaluated in women treated with drug combinations that did not include procarbazine. Ovarian function was normal in all of six women treated for

non-Hodgkin's lymphoma with a cyclophosphamide containing drug combination (90). Others reported that pubertal progression was adversely affected in 5.8% of 17 patients treated before puberty, compared to 33.3% of 18 patients treated during puberty or after menarche. However, the administration of cyclophosphamide did not correlate with the abnormal pubertal progression observed in these patients (91). Cis-platinum administration resulted in amenorrhea in 14% of seven patients (92).

Chemotherapy with doxorubicin, cyclophosphamide and high-dose methotrexate produced irregular menses in 20% of five women, and persistent amenorrhea in 20% of five women treated for soft tissue sarcomas (93). Therapy with high-dose methotrexate (250 mg/kg/dose), with or without vincristine, did not cause ovarian failure in any of four women evaluated after the completion of therapy (94). Treatment with nitrosoureas, with or without procarbazine, produced ovarian damage in young women treated with craniospinal irradiation for malignant brain tumors (95).

Women who received high dose (50 mg/kg/day x 4 days) cyclophosphamide prior to bone marrow transplantation for aplastic anemia all developed amenorrhea following transplantation. In one series, 36 of 43 had recovery of normal ovarian function 3 – 42 months after transplantation (66).

Loss of ovarian function following chemotherapy administration to post-menarcheal patients is associated with significant changes in libido and sexual function (96). Recovery of ovarian function is unlikely if menstrual periods do not return within three months after cessation of treatment (97).

The presence of apparently normal ovarian function at the completion of chemotherapy should not be interpreted as evidence that no ovarian injury has

occurred. Premature menopause is well documented in childhood cancer survivors. Women diagnosed after 12 years of age were significantly more likely to be menopausal during the interval 21 to 30 years of age than their sibling controls (RR – 2.32, 95% confidence interval (CI) - 1.63, 3.29). Women treated for Hodgkin disease had a significantly increased risk of menopause compared to their siblings (RR - 3.35, 95% CI – 2.06, 5.47), a risk that increased if treatment included both radiation therapy below the diaphragm and use of an alkylating agent (RR – 9.57, 95% CI – 4.93, 18.69) (98). When the pelvis is excluded from the treatment volume, and treatment does not include combination chemotherapy, premature menopause is infrequent (99).

Testicular Damage

Surgery, irradiation and/or chemotherapy may damage testicular function. Retrograde ejaculation is a frequent complication of bilateral retroperitoneal lymph node dissection performed on males with testicular neoplasms (100,101), and impotence may occur following extensive pelvic dissections as may be performed to remove a rhabdomyosarcoma of the prostate (102).

One of the first studies of the effects of testicular irradiation on spermatogenesis was conducted using inmate volunteers from the Oregon State Penitentiary who underwent vasectomy at the completion of the radiation experiments. Complete recovery of spermatogenesis was observed 9 - 18 months after treatment in those treated with 100 cGy, by 30 months in those treated with 200 or 300 cGy, and after 60 or more months in those treated with 400 or 600 cGy (103,104).

Men treated with whole abdomen irradiation may develop gonadal dysfunction. Five of ten men were azoospermic, and two were severely oligospermic when evaluated

at ages 17 - 36 years following treatment with whole abdomen irradiation for Wilms tumor at ages 1 - 11 years, with the penis and scrotum either excluded from the treatment volume, or shielded with 3 mm of lead. The testicular radiation doses varied from 796 - 983 cGy (105). Others reported azoospermia in 100% of ten men 2 - 40 months after radiation therapy doses of 140 - 300 cGy to both testes (106). Similarly azoospermia was demonstrated in 100% of ten men following testicular radiation therapy doses of 118 - 228 cGy. Recovery of spermatogenesis occurred after 44 - 77 weeks in 50% of the men, although three of the five with recovery had sperm counts below 20 x 10^6/ml (107). Oligo- or azoospermia was reported in 33% of 18 men evaluated 6 - 70 months after receiving testicular radiation doses of 28 - 135 cGy (45). In another report, none of five men who received testicular radiation doses of less than 20 cGy became azoospermic. By contrast, two who received testicular radiation doses of 55 - 70 cGy developed temporary oligospermia, with recovery to sperm counts greater than 20 x 10^6/ml 18 - 24 months after treatment (109).

Administration of higher doses, such as 2400 cGy which is used for the treatment of testicular relapse of acute lymphoblastic leukemia, results in both sterilization and Leydig cell dysfunction (110). Craniospinal irradiation produced primary germ cell damage in 17% of 23 children with acute lymphoblastic leukemia (111), but in none of four children with medulloblastoma (112). With adequate shielding, gonadal failure following radiation therapy to a volume that does not include the testis is infrequent (113).

Combination chemotherapy that includes an alkylating agent and procarbazine causes severe damage to the testicular germinal epithelium (Table 7)

(82,83,84,114,115, 116,117,118,119,120,121,122,123). Azoospermia was present in all men by the start of the third cycle of MVPP chemotherapy (119), and less than 20% of men had recovery of spermatogenesis when evaluated 37- 48 months after treatment, suggesting that recovery of spermatogenesis in this population of patients was infrequent (118). Azoospermia occurred less frequently following treatment with two, rather than six, cycles of MOPP (Table 8) (124), and elevation of the basal FSH level, reflecting impaired spermatogenesis, was less frequent among patients receiving two courses of OPPA (vincristine, procarbazine, prednisone, Adriamycin), than among those who received two courses of OPPA in combination with two or more courses of COPP (cyclophosphamide, vincristine, procarbazine and prednisone) (125).

Most studies suggest that procarbazine contributes significantly to the testicular toxicity of combination chemotherapy regimens. The combination of doxorubicin, bleomycin, vinblastine and DTIC produced oligo- or azoospermia frequently during the course of treatment. However recovery of spermatogenesis occurred after treatment was completed, in contrast to the experience reported following treatment with MOPP (120).

An early report suggested that the prepubertal testis was less sensitive than the postpubertal testis to damage by MOPP chemotherapy (117). Several groups of investigators reported that damage to the prepubertal testis could not be identified until the patient entered puberty, if the frequency of testicular damage was estimated by the presence of an elevated serum FSH level (114,126,127,128,129). None of these studies reported that prepubertal males were at lower risk for chemotherapy induced testicular damage than were postpubertal patients.

Treatment for non-seminomatous germ cell tumors of the testis usually includes the combination of cis-platinum, vinblastine and bleomycin. Oligospermia or azoospermia was reported in most men following treatment with this chemotherapy regimen, with azoospermia still present in 25% - 30% of men 24 - 94 months after completion of treatment (130,131,132). Interpretation of these results, as well as those in men with Hodgkin disease is complicated by the high frequency of oligo- or azoospermia in these patients prior to initiation of treatment (133,134,135,136,137).

Testicular function was evaluated in patients following treatment with combination chemotherapy for acute lymphoblastic leukemia during childhood. Basal serum FSH and LH levels were normal in 32 prepubertal boys evaluated, whereas 37.5% of eight early pubertal, and 50% of four late pubertal subjects had raised basal serum FSH levels (138). The factors that influenced the severity of testicular damage were the total dose of cyclophosphamide, administration of a cumulative dose of cytosine arabinoside that exceeded 1 gm/M^2, and the length of time between the cessation of treatment and testicular biopsy (139). Blatt et al. reported normal testicular function in 14 boys treated for ALL with therapy which did not include either cyclophosphamide or intravenous cytosine arabinoside, emphasizing the importance of the agents employed in determining the gonadal toxicity of a combination chemotherapy program (140).

Three of the four men treated with high-dose methotrexate for osteosarcoma had normal sperm counts, whereas the fourth was severely oligospermic when first evaluated after cessation of treatment (94). Treatment of men with doxorubicin, cyclophosphamide and high-dose methotrexate for soft tissue sarcoma produced

azoospermia in 100% of eight men following chemotherapy and proximal radiotherapy, 25% of eight men following chemotherapy and distal radiotherapy, and 20% of five men treated with chemotherapy only. Recovery of spermatogenesis was documented in men treated with chemotherapy only, or chemotherapy and distal radiation, whereas azoospermia persisted in those men treated with chemotherapy and proximal radiotherapy (141). Similar results have been reported in male survivors of non-Hodgkin lymphoma, in whom pelvic radiation therapy and cumulative cyclophosphamide dose greater than 9.5 gm/M^2 were independent determinants of failure to recover spermatogenesis (142); and in survivors of Ewing and soft tissue sarcoma, in whom treatment with a cumulative cyclophosphamide dose greater than 7.5 gm/M^2 was correlated with persistent oligo- or azoospermia (143). Kenney and her colleagues reported that 66.7% (10/15) of males treated with > 7.5 gm/M^2 of cyclophosphamide were oligo- or azoospermic (144).

Fertility

The fertility of survivors of childhood cancer, when evaluated in aggregate, is impaired. The adjusted relative fertility of survivors, compared to that of their siblings was 0.85 (95% CI - 0.78 - 0.92). The adjusted relative fertility of male survivors (0.76, 95% CI - 0.68 - 0.86) was slightly lower than that of female survivors (0.93, 95% CI - 0.83 - 1.04). The most significant differences in the relative fertility rates were demonstrated in male survivors who had been treated with alkylating agents, with or without infradiaphragmatic irradiation (145).

Fertility may be impaired by factors other that the absence of sperm and ova. Conception requires delivery of sperm to the uterine cervix and patency of the Fallopian

tubes for fertilization to occur and appropriate conditions in the uterus for implantation. Retrograde ejaculation occurs with a significant frequency in men who undergo bilateral retroperitoneal lymph node dissection. Uterine structure may be affected by abdominal irradiation. A recent study demonstrated that uterine length was significantly less in ten women with ovarian failure who had been treated with whole abdomen irradiation. Endometrial thickness did not increase in response to hormone replacement therapy in three women who underwent weekly ultrasound examination. No flow was detectable with Doppler ultrasound through either uterine artery of five women, and through one uterine artery in three additional women (146,147). Similarly four of eight women who received 1440 cGy of total body irradiation had reduced uterine volume and undetectable uterine artery blood flow (148). These data are pertinent when considering the feasibility of assisted reproduction for these survivors.

Pregnancy Outcome

Most chemotherapeutic agents are mutagenic, with the potential to cause germ cell chromosomal injury. Possible results of such injury include an increase in the frequency of genetic diseases and congenital anomalies in the offspring of successfully treated childhood and adolescent cancer patients.

Several early studies of the offspring of patients treated for diverse types of childhood cancer identified no effect of previous treatment on pregnancy outcome and no increase in the frequency of congenital anomalies in the offspring (149,150,151). However a study of offspring of patients treated for Wilms tumor demonstrated that the birthweight of children born to women who had received abdominal irradiation was significantly lower than that of children born to women who had not received such

irradiation (152), a finding that was confirmed in several subsequent studies (153,154,155). The abnormalities of uterine structure and blood flow reported following abdominal irradiation might explain this clinical finding.

Prior studies of offspring of childhood cancer survivors were limited by the size of the population of offspring and the number of former patients who had been exposed to mutagenic therapy. Several recent studies which attempted to address some of these limitations did not identify an increased frequency of major congenital malformations (151,156,157,158,159,160,161,162), genetic disease (151) or childhood cancer (162,163,164) in the offspring of former pediatric cancer patients, including those conceived after bone marrow transplantation (165). However there are preliminary data suggesting a deficit of males in the offspring of male survivors in the Childhood Cancer Survivor Study cohort (166).

In general the studies of pregnancy outcome following treatment with chemotherapeutic agents are reassuring with respect to the possible increased occurrence of congenital malformations or genetic diseases in the offspring. However the number of exposed patients available for study is still small, and the follow-up of those offspring who have been identified is short, precluding definitive statements regarding the risk of cancer in the offspring.

Gonadal Protection

Protection of the ovary using oral contraceptive agents and luteinizing hormone releasing hormone agonists was evaluated in women treated with MVPP. One study demonstrated that permanent amenorrhea did not occur in six women, aged 18 – 31 years, who received an oral contraceptive during the period of treatment with MVPP

(167), although two subsequently developed premature menopause, and another had a menopausal gonadotropin pattern (87). Another study of nine women aged 20 – 28 years was unable to demonstrate a protective effect of oral contraceptive administration on the ovarian function of women treated with MVPP (81). Amenorrhea occurred in all eight women, aged 17 - 34 years, treated with a luteinizing hormone releasing hormone (LHRH) agonist (Buserelin), and three of ten MVPP treated control women. Four of the Buserelin treated women had recovery of ovarian function after therapy with MVPP was completed (168).

Buserelin administration was evaluated for protection of the testis. No protective effect, as estimated by post-therapy sperm count, was evident in 20 Buserelin treated men, when compared to ten control men (168). Similarly no protective effect of treatment with another LHRH agonist, D-Trp6-Pro9-N-ethylamide-LHRH (LH-RHa), on spermatogenesis was demonstrated in six men following treatment with MOPP (169).

SECOND MALIGNANT NEOPLASMS

Second malignant neoplasms (SMNs) are a recognized complication of successful treatment of children and adolescents for cancer. The frequency of these had been reported to be 2.6% - 12.1% at 25 years after diagnosis (170,171,172,173,174,175,176). These series differed in the time period during which the patients were treated, the completeness of follow-up and the treatment exposures experienced by the patients. Increasingly the data suggest that, although specific exposures, whether to a particular chemotherapeutic agent or to ionizing radiation, may be linked to the occurrence of a new malignancy, the most important factor in the

pathogenesis of many SMNs, previously suspected, but until recently poorly documented, may be the genetic susceptibility of the patient.

Genetic Factors

The importance of genetic predisposition to the occurrence of a SMN has been demonstrated most clearly in patients with hereditary retinoblastoma. Among 1,604 children treated for retinoblastoma at several medical centers in Boston, Massachusetts between 1937 and 1984, and several medical centers in New York, New York between 1914 and 1984, who survived for one year after diagnosis, 961 had the hereditary form of the disease. The cumulative percentage who developed a SMN was 51.0% (± 6.2%) fifty years after retinoblastoma diagnosis, compared to 5.0% (± 3.0%) among those with nonhereditary retinoblastoma. Among those patients with hereditary retinoblastoma, the cumulative percentage who developed a SMN was 58.3% (± 8.9%) among those whose treatment included radiation therapy, compared to 26.5% (± 10.7%) among those whose treatment did not include radiation therapy (177,178).

Others, although confirming the susceptibility of patients with hereditary retinoblastoma to the development of new cancers, did not identify an effect of the same magnitude as that reported by Abramson and his colleagues. Draper, in a report based upon the experience of the Oxford Childhood Cancer Research Group, estimated the risk of a SMN following treatment for retinoblastoma was 4.2% 18 years after diagnosis among all patients with retinoblastoma, and 8.4% 18 years after diagnosis among those with genetic retinoblastoma (179). The rate reported among patients with genetic retinoblastoma was approximately one-fifth the rate reported by Abramson. The explanation for this difference in the rates of SMNs is not clear, but may be related to

differences in the frequency of administration of chemotherapy, especially alkylating agents, to these patients, biased follow-up of patients who developed a second malignant tumor or differences in the median duration of follow-up of the two series. Chemotherapy was administered to 6.7% (26/384) of the British patients with genetic retinoblastoma (179) and to an unreported fraction of the American patients (177).

The Li-Fraumeni syndrome consists of sarcoma diagnosed in the proband prior to age 45 years, with additional cancers, frequently soft tissue sarcoma or breast cancer, diagnosed in other children and young adults within the family (180). The genetic defect in some families with the Li-Fraumeni syndrome was demonstrated to be a mutation within the p53 gene (181,182,183,184), and in others to be due to mutations of CHK2 (185,186). Because the pattern of first and second malignant tumors in some patients with SMNs resembled the distribution observed within some families with the Li-Fraumeni syndrome, a series of patients with SMNs was evaluated for the occurrence of mutations at this locus. Mutations were identified in 5.1% of 59 patients examined (187). Mutations within the p53 gene have been demonstrated in neurofibrosarcomas, but not the germline, of some patients with neurofibromatosis type 1 (NF1)(188). Future research may demonstrate that those NF1 patients who develop SMNs have coexistent germline p53 mutations.

Genetic loci associated with the occurrence of Wilms tumor have been identified at 11p13 (WT1) and 11p15. Some patients have germline mutations in WT1, the only Wilms tumor associated gene that has been sequenced (189,190). Li et al. reported that the frequency of SMNs in a cohort of successfully treated Wilms tumor patients was 6% ($\pm$ 6%) 20 years after diagnosis. SMNs were diagnosed only in irradiated patients.

Patients who had received dactinomycin were not protected from the occurrence of SMNs (191), in contrast to the results of a prior case-control study (192). Breslow et al. reviewed the occurrence of SMNs among patients entered on the National Wilms Tumor Studies. The cumulative risk of a SMN was 1.6% 15 years after diagnosis. The relative risk of developing a SMN was increased in patients who had received radiation therapy, with the relative risk increasing with increasing radiation dose. Administration of doxorubicin increased the relative risk at each level of radiation exposure (193).

One group of investigators reported SMNs in 33.3% (2/6) of patients with bilateral Wilms' tumor (194), a group of patients, many of whom would be expected to have germline abnormalities in a Wilms tumor associated gene, but patients with bilateral Wilms tumor were not at increased risk for a SMN in the National Wilms Tumor Study Group analysis (193).

Treatment Factors

Surgery

Surgical procedures can increase the risk of subsequent malignancy. Adenocarcinoma of the colon was reported in several patients following ureterosigmoidostomy. The incidence rate of adenocarcinoma in these patients was approximately 9.9/1000 compared to an incidence rate of 9.9/100,000 in the general population (195). The majority of reported patients have undergone this procedure for treatment of exstrophy of the bladder. The median number of years between ureterosigmoidostomy and the diagnosis of colon carcinoma was 22 (196). Carcinoma may develop at the uretero-colonic suture line following temporary ureterosigmoidostomy despite rediversion of urine away from the colonic mucosa (197),

and was reported in one patient with ileal loop urinary diversion (198), suggesting that the complication may not be avoided by the use of a different surgical procedure.

Radiation Therapy

Thyroid carcinoma is a known complication of neck irradiation during infancy for benign conditions (199). Patients who receive neck irradiation for malignant diseases are at risk for the subsequent occurrence of thyroid malignancies. These have been reported following treatment of patients with medulloblastoma (200,201,202), rhabdomyosarcoma (203), acute lymphoblastic leukemia (203,204) and Hodgkin disease (205,206,207,208,209,210,211). The incidence of thyroid cancer in survivors of Hodgkin disease was 0.8% (1/119) among children treated at SUMC (212).

Thyroid carcinoma was the most frequently diagnosed SMN in a series of survivors of Hodgkin disease treated during childhood and adolescence at Roswell Park Cancer Institute (RPCI). The standardized incidence ratio (SIR) was 158.75 (95% CI 32.74 - 463.93) among males, and 38.02 (95% CI 7.84 - 111.11) among females (213). The SIR for thyroid cancer among males in the five Nordic countries study was 55 (95% CI 15 - 140), and was 25 (95% CI 8 - 57) among the females (214). The SIR for males and females combined who were treated at SUMC was 9.7 (95% CI 2.4 - 26.4) (215), and was 32.7 (95% CI 15.3 - 55.3) among patients reported by the LESG (216). The SIR for thyroid cancer was not estimated in the remaining studies of SMNs in survivors of Hodgkin disease diagnosed during childhood or adolescence.

Central nervous system tumors, including meningiomas and gliomas, have been reported with increasing frequency following direct or incidental irradiation of the brain (217,218,219,220,221), a finding that was anticipated based on the occurrence of brain

tumors in children treated with low doses of radiation therapy for tinea capitis (222). Neglia and his colleagues reported that the RR of a secondary central nervous system malignancy among children treated for acute lymphoblastic leukemia was 21.7. The most significant factors for the occurrence of these tumors were previous prophylactic cranial irradiation and age less than 6 years at diagnosis (223).

Sarcomas of bone have been reported both in patients with hereditary retinoblastoma, and those surviving other types of childhood cancer. The cumulative risk of a SMN in bone was estimated to be 2.8% among 9170 patients evaluated, but was 14.1% among those with retinoblastoma and 22.1% among those treated for Ewing sarcoma at 20 years after diagnosis (224). The RR was 2.7 among patients whose treatment included radiation therapy, with the RR increasing with increasing radiation therapy dose and more intensive use of alkylating agents (224). Hawkins and his colleagues calculated the cumulative frequency of bone cancer in previously irradiated childhood cancer survivors was 0.5% among those not treated for retinoblastoma and was 7.2% among those treated for heritable retinoblastoma (225). The dramatic risk of sarcoma of bone following treatment of Ewing sarcoma, reported earlier from several single institutions (226,227), was confirmed in a multi-institutional review. The cumulative frequency of a SMN in successfully treated patients was 9.2% at 20 years after diagnosis, and that of a secondary sarcoma was 6.5%. No secondary sarcomas developed in patients who had received less than 4800 cGy (228).

The evolution of radiation therapy technique from the use of orthovoltage radiation apparatus that produce a higher absorbed dose in bone to the use of megavoltage radiation apparatus that does not have this characteristic should result in a

lower frequency of SMNs in irradiated bones (229,230). However when this question was addressed in a case-control study of bone sarcoma as a SMN, no difference in the relative risk for patients treated with orthovoltage, compared to megavoltage, radiation therapy could be demonstrated (224).

Successfully treated patients are at risk of developing carcinomas within prior radiation therapy treatment volumes at a very early age (e.g. the skin) (231). Breast cancer was reported in three young women (22, 34 and 38 years of age) following irradiation for Wilms tumor to a volume that included part or all of the breast (232,233), and is a frequent SMN following treatment for Hodgkin disease. The SIR for breast cancer among patients treated at RPCI was 7.77 (95% CI 2.12 - 19.89) (213). Although elevated significantly, it is not as dramatically increased as in other series, such as that from SUMC (26.2, 95% CI 15 - 42.6) (215), SJCRH (33.2, 95% CI 12.1 - 72.4) (234), the Late Effects Study Group (75.3, 95% CI 44.9 - 118.4) (235), the Statistics, Epidemiology and End Results Program (60.57, 95% CI 22.1 - 132) (236), or the Nordic countries 17 (95% CI 9.9 - 28) (214).

Adenocarcinoma of the colon occurred within the volume of irradiation in three patients at the ages of 12, 27 and 27 years (237,238,239). It is possible that these patients had germline mutations in a cancer predisposition gene that contributed to their susceptibility to radiation carcinogenesis.

Total body irradiation, a component of most preparative regimens for allogeneic bone marrow transplantation for malignant diseases, is associated with a cumulative risk for the occurrence of a second solid neoplasm of 8.3% at 13 years after treatment (240).

Chemotherapy

The significance of prior treatment with chemotherapy in the pathogenesis of SMNs was first evaluated in detail in cohorts of adults treated successfully for Hodgkin disease. The risk factors for the occurrence of SMNs in pediatric patients following treatment for Hodgkin disease have been less thoroughly evaluated.

Bhatia et al. reported that the cumulative risk of developing any SMN following treatment for Hodgkin disease in childhood was 7% at 15 years after diagnosis. The risk of developing non-Hodgkin lymphoma was 1.1%, and of any type of leukemia was 2.8% at fifteen years after diagnosis. They calculated the cumulative dose/square meter of each alkylating agent received, divided the cumulative dose distributions for each agent into thirds, and assigned a numerical value for each agent received (0,1,2,3) depending on whether the patient had received none of the drug, or had a cumulative drug dose in the lower, middle or upper third of the dose distribution. A summary score (alkylating agent dose (AAD) score) was derived by adding the results for each agent received. The relative risk of leukemia increased by 1.5 for each unit increase in the AAD score (235,241). The actuarial risk of developing acute myelogenous leukemia 10 years after diagnosis was 11%(± 7%) among pediatric patients treated at SUMC with low-dose (2500 cGy) radiation therapy and MOPP chemotherapy, which has an AAD score of 2 (242), and was 1.1% 15 years after diagnosis among pediatric patients treated with involved or extended field radiation therapy and various chemotherapy regimens that did not contain nitrogen mustard (vincristine, prednisone, doxorubicin, with or without procarbazine; cyclophosphamide, vincristine, prednisone, procarbazine or

methotrexate) (243). Prior treatment with an alkylating agent has been shown to modify the risk of developing bone cancer (224) or leukemia (244) as a SMN.

The epipodophyllotoxins have been identified as important leukemogens. Pui et al. reported the risk of secondary acute myelogenous leukemia (AML) was 4.7% at six years after diagnosis among patients treated for acute lymphoblastic leukemia. The risk was substantially higher (19%) among patients with T-cell leukemia (245). These investigators subsequently demonstrated that the risk of secondary AML in this population was related to the administration of epipodophyllotoxins, with the cumulative frequency of AML being 12.3% among those treated twice weekly and 12.4% among those treated weekly, compared to 1.6% among those treated with the drug less frequently or not at all (246).

The risk of secondary AML depends upon the cumulative dose of drug administered, as well as the schedule of administration, with the frequency reported to be zero percent among germ cell tumor patients treated with less than 2000 mg/M^2 (247), 5.9% among childhood acute lymphoblastic leukemia patients treated with 1,800 - 9,900 mg/M^2 (248), 11.3% among germ cell tumor patients who received more than 2000 mg/M^2 (247), and 18.4% among pediatric non-Hodgkin lymphoma patients who received 4,200 -5,600 mg/M^2 (249). Hawkins and his colleagues reported an increasing risk of secondary leukemia with increasing cumulative dose of epipodophyllotoxin, but did not find that the risk of secondary leukemia was zero for cumulative doses below 2000 mg/M^2 (250).

The leukemogenicity of topoisomerase II inhibitors may be related to the high degree of specificity of these agents for specific DNA targets including the

myeloid-lymphoid leukemia (MLL) gene (251,252) and the acute myeloid leukemia 1 (AML1) gene (253).

The carcinogenic potential of the anthracycline, doxorubicin, was suggested by the results of a previous case-control study of risk factors for leukemia as a SMN, in which increasing doxorubicin dose was associated with an increasing RR of leukemia as a SMN after adjustment for the AAD score (244). This finding is of interest, as doxorubicin is now known to have topoisomerase II as one of its targets, the same target as that of the epipodophyllotoxins. A similarly conducted case-control study of risk factors for bone sarcoma as a SMN did not identify any effect of doxorubicin therapy on the risk of developing such SMNs (224). An analysis of risk factors for any SMN in a large cohort of childhood cancer patients demonstrated that treatment with doxorubicin was the only factor identified, in addition to treatment with BCNU, that increased the risk of a SMN (175), a finding apparently extending the earlier suggestion that doxorubicin was leukemogenic. Neglia and his colleagues, in a study of 13,581 childhood cancer survivors treated at 25 institutions, demonstrated an independent trend for increasing SMN risk with increasing cumulative exposure to epipodophyllotoxins ($p = 0.02$) and anthracyclines ($p = 0.02$) (254).

Although most studies of carcinogenicity of chemotherapeutic agents have focused on the development of leukemia following treatment, it is clear that solid tumor induction is also possible following exposure to one or more chemotherapeutic agents. The best example of this is the occurrence of solid SMNs in genetically predisposed retinoblastoma patients who were treated with cyclophosphamide only following enucleation (179). As our ability to identify genetically predisposed patients improves,

our understanding of the apparent anomaly of solid tumor induction following systemic exposure to a carcinogenic agent will increase.

Immune Suppression

Immune suppression is a component of allogeneic bone marrow transplantation. To prevent graft versus host disease, antithymocyte globulin (ATG) may be administered to the recipient or the bone marrow may be manipulated to remove T-cells. These manipulations and bone marrow transplantation from an unrelated bone marrow donor increase the risk of Epstein-Barr virus associated B-cell lymphoproliferative disorder. The cumulative incidence rates at ten years after bone marrow transplantation were 11.3% among those treated with ATG, 11.4% among those who received T-cell depleted bone marrow, and 2.3% among those who received bone marrow from unrelated donors (240).

RECOMMENDATIONS

Three of the major issues of concern to survivors of childhood cancer are the effect of treatment on mortality, particularly premature morality due to cardiac disease or SMNs; and the effect of treatment on fertility and offspring.

There is a substantial body of data regarding the late effects of radiation therapy on cardiac function. Most of these data have been obtained from patients who received treatments that are no longer used. There are scant data regarding the effects of low dose radiation therapy (1500 – 2500 cGy) on the rate of coronary artery disease or valvular disease in survivors of pediatric Hodgkin disease. Cohorts that have received low dose radiation therapy need to be identified, and followed to determine the frequency of these late end points.

Anthracycline cardiomyopathy is an important cause of late morbidity and mortality. There are no evidence-based guidelines at present regarding the type, frequency or duration of cardiac follow-up for these patients. Intervention studies are difficult to conduct as the result of the mobile nature of the adult population of childhood cancer survivors – those who are at greatest risk for late events related to earlier anthracycline therapy. Well-executed cohort studies are needed to address the questions regarding screening strategy, and the efficacy of interventions. The interaction of anthracycline related abnormalities with other risk factors, such as hypertension, hyperlipidemia, smoking and obesity, needs to be further evaluated.

Fertility and pregnancy outcomes have been studied in several large cohorts. Remaining questions relate to the effect, if any, of various chemotherapy treatments on the frequency of birth defects or cancer in the offspring. Despite the large size of recent cohorts, statistical power may still be limited when the effects of agents such as nitrogen mustard or procarbazine on birth defect rates are evaluated in populations frequently rendered sterile by these agents. Preservation of fertility is an emerging area of intervention that has potential, but additional practical and ethical concerns (255,256,257).

The risk factors for second malignant neoplasms have been studied in some detail. Important areas for future research include the conduct of studies in which the cases are well characterized with respect to the presence or absence of cancer predisposition genes, drug activation and degradation enzyme alleles, and treatment exposures. Such studies may lead to new insights that allow the conduct of targeted interventions studies. In addition effective interventions to prevent smoking initiation

must be developed for childhood cancer survivors who smoke at rates similar to the general population (222,223,224,225,226,227).

Post therapy fatigue has been inadequately studied in adult survivors of pediatric and adolescent cancer. It has been reported in 33% of five-year survivors of adult cancer (258). Qualitative research regarding fatigue in childhood and adolescent cancer patients has been initiated (259), but much additional research is necessary to define the extent of this problem and to develop appropriate interventions.

TABLE 1

RELATIONSHIP BETWEEN RADIATION PERICARDITIS AND

THE WHOLE PERICARDIUM RADIATION DOSE

	Dose (cGy)			
	<599	600 - 1500	1501 - 3000	>3000
Pericardial Irradiation (Number of Patients)	198	42	123	14
Pericarditis	14(7.1%)	5(11.9%)	3(18.7%)	7(50%)
Pericarditis Requiring Treatment	3(1.5%)	4(9.5%)	8(6.5%)	5(35.7%)

TABLE 2

FREQUENCY OF CONGESTIVE HEART FAILURE

IN PATIENTS TREATED WITH DOXORUBICIN

	Weekly Schedule		Every Three Week Schedule	
Cumulative Dose (mg/M^2)	0 - 14*	40 - 59*	0 - 14*	40 - 59*
100	0.1%	0.2%	0.4%	0.7%
200	0.2%	0.3%	0.9%	1.3%
300	0.4%	0.6%	1.5%	2.2%
400	0.5%	0.7%	1.9%	2.3%
500	1.0%	1.5%	3.8%	5.8%
600	2.6%	3.9%	10.0%	14.9%
700	5.7%	8.7%	21.2%	30.5%

* - Age in Years

TABLE 3

RELATIONSHIP BETWEEEN OVARIAN RADIATION DOSE AND

THE OCCURRENCE OF AMENORRHEA

RADIATION DOSE (cGy)	AMENORRHEA
0 – 100	16% (1/6)
101 – 200	14% (1/7)
201 – 300	12% (1/8)
301 – 400	25% (1/4)
401 – 500	44% (4/9)
501 – 600	50% (3/6)
601 – 700	25% (1/4)

TABLE 4

FREQUENCY OF AMENORRHEA FOLLOWING

TREATMENT WITH COMBINATION CHEMOTHERAPY

PATIENT AGE	REGIMEN	FREQUENCY OF AMENORRHEA
All ages	MVPP	63% (20/32)
All ages	MOPP	39% (17/44)
All ages	ChlVPP	19% (6/32)
All ages	ChlVPP/EVA	80% (16/20)

TABLE 5

RELATIONSHIP BETWEEN AGE AT TREATMENT AND FREQUENCY OF AMENORRHEA FOLLOWING TREATMENT WITH COMBINATION CHEMOTHERAPY

PATIENT AGE	REGIMEN	FREQUENCY OF AMENORRHEA
< 30 years	MVPP	52% (17/33)
30 - 51 years		86% (31/36)
< 25 years	MOPP	20% (3/15)
> 25 years		89% (8/9)
<30 years	MOPP	0% (0/10)
30 - 40 years		50% (5/10)

TABLE 6

RELATIONSHIP AMONG AGE AT TREATMENT, NUMBER OF CYCLES AND FREQUENCY OF AMENORRHEA FOLLOWING TREATMENT WITH COMBINATION CHEMOTHERAPY

PATIENT AGE	NUMBER OF CYCLES	REGIMEN	FREQUENCY OF AMENORRHEA
16 - 30 years	3	MOPP	3% (1/31)
	6		9% (1/11)
31 - 45 years	3		61% (11/18)
	6		62% (5/8)

TABLE 7

FREQUENCY OF AZOOSPERMIA FOLLOWING

COMPLETION OF COMBINATION CHEMOTHERAPY

TREATMENT REGIMEN	FREQUENCY OF AZOOSPERMIA
MOPP	75% (42/56)
M(O/V)PP,COPP	87% (5/6)
MVPP	86% (132/154)
COPP	100% (106/106)
ChlVPP	100% (11/11)
ChlVPP/EAV	95% (21/22)
ABVD	0% (0/13)

TABLE 8

RELATIONSHIP BETWEEN NUMBER OF CHEMOTHERAPY CYCLES AND THE FREQUENCY OF AZOOSPERMIA AFTER COMBINATION CHEMOTHERAPY

TREATMENT REGIMEN	NUMBER OF CYCLES	FREQUENCY OF AZOOSPERMIA
MOPP	2	0% (0/7)
	6	90% (9/10)

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