REVIEW
Obesity in Pediatric Oncology

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Today's obesity pandemic began in the United States, spread to Western Europe and other developed regions, and is emerging in developing countries. Its influences on outcomes of childhood cancer are unknown. A recent Children's Oncology Group symposium considered epidemiology of obesity, pharmacology of chemotherapy and outcomes in obese adults with cancer, excess mortality in obese pediatric patients with acute myeloid leukemia (AML), and complications in obese survivors. The salient points are summarized herein. Body mass index (BMI) is the accepted index of weight for height and age. In the US, obesity prevalence (BMI > 95th centile) is increasing in all pediatric age groups and accelerating fastest among black and Hispanic adolescents. Pharmacologic investigations are few and limited: half-life, volume of distribution, and clearance in obese patients vary between drugs. Obese adults with solid tumors generally experience less toxicity, suggesting underdosing. For patients undergoing bone marrow transplantation, obese adults generally experience greater toxicity. In pediatric acute myeloblastic leukemia, obese patients have greater treatment-related mortality (TRM), similar toxicity and relapse rates, and inferior survival compared with patients who are not obese. An excess of female survivors of childhood leukemia who received cranial irradiation are obese. Ongoing treatment effects of childhood cancer may predispose to a sedentary lifestyle. These findings call for measures to prevent obesity, retrospective and prospective studies of chemotherapy pharmacology of analyzed according to BMI and outcomes, additional studies of the obesity impact on outcomes in pediatric cancer, and promotion of a healthy lifestyle among survivors. Pediatr Blood Cancer 2005;45:881–891. © 2005 Wiley-Liss, Inc.

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INTRODUCTION

In North America, Western Europe, Australia, New Zealand, and parts of the Middle East, obesity is now a more important form of malnutrition than undernutrition, and in some rapidly developing countries, such as China, obesity is an emerging problem. The problem of obesity is manifest in pediatric oncology patients at diagnosis, during treatment, and after treatment. The effects of obesity on outcomes of children with cancer are just now being recognized. The Nutritional Committee of the Children's Oncology Group decided that obesity in children with cancer warranted further discussion. A symposium was held in November 2003 to discuss the issues. This review highlights the presentations from that meeting with an emphasis on the epidemiology of obesity, bioavailabilty and distribution of chemotherapy in obese adults, and outcomes in obese adults with cancer, survival in pediatric acute myeloid leukemia (AML) in obese patients, and the prevalence and consequences of obesity among long-term pediatric cancer survivors.

OBESITY PANDEMIC

A pandemic as defined in Webster dictionary is an outbreak of disease occurring over a wide geographic area and affecting an exceptionally high proportion of the population. In these terms, the United States is experiencing a pandemic of obesity. Globally, where the focus in the past has been on under nutrition, obesity is surfacing as a significant health issue in developed and developing countries [1]. Assessment of the extent of obesity around the globe is complicated by varying trends of obesity in different countries based on diverse of socioeconomic factors, coexistence of ongoing significant undernutrition, and variable health responses to degrees of overweight [2,3]. This introduction will try to put into perspective the severity and extent of excessive weight in American children and adults.

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To understand the problem, it is important to define categories of excessive weight. Body mass index (BMI) is the current accepted measure of appropriateness of weight for a given height. It is calculated by dividing weight in kilograms by height in square meters (BMI = kg/m^2) [4]. In adults, a BMI of 25 to 29.9 kg/m^2 is classified as overweight and a BMI $\geq$ 30 kg/m^2 is defined as obese. In growing children, distribution of BMI changes significantly with age, so BMI centiles by age are used to classify the appropriateness of weight in children [5,6]. Hence, while a BMI of 22 is perfectly acceptable in an adult, a BMI of 22 in a 7-year-old girl places her above the 95th centile. Also, the term "obesity" is not used to define children; it is a measure of adiposity rather than a description of weight for height for age. Instead children are classified as overweight if BMI is greater than the 95th centile and "at risk of overweight" if BMI is between the 85th and 95th centiles.

Between 1991 and 1999, obesity (BMI $\geq$ 30 kg/m^2) prevalence rates among adults increased by more than half [7]. Flegal et al. [8] continuously sampled National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2000 and found that, the obese group increased from 22.9% to 30.5% between 1988 and 1994 in NHANES III ($P < 0.001$). In NHANES III, 55.5% of adults had a BMI $\geq$ 25; by 2000 this number was 64.5% ($P < 0.001$).

The weight gain in children mirrors that of adults. Table I shows the increase in the proportion of overweight children over the past three decades. Ogden evaluated the 1999–2000 sampling of continuous NHANES pediatric data and found an alarming rate of at-risk for overweight and overweight for all age groups (Table II): 20.6% of 2–5 year olds, 30.3% of 6–11 year olds, and 30.4% of 12–19 year olds were either overweight or at risk of overweight [9]. Prevalence rates for overweight were 10.4% in 2–5 year olds, 15.3% in 6–11 year olds, and 15.5% in 12–19 year olds (Table II). By bell curve distribution, <5% of the population should fall in the >95th centile.

Significant increases in percentages of overweight adolescents 12–19 years old between NHANES II (1988–1994) and NHANES III (1999–2000) were noted in non-Hispanic Black males ($P < 0.001$), Mexican American males ($P < 0.001$), and non-Hispanic Black females ($P = 0.002$) (Table III) [9,10]. In a prospective study of children aged 4–12 enrolled in the National Longitudinal Survey of Youth, 21.5% of black youths, 21.8% of Hispanic youths, and 12.3% of non-Hispanic White youths had BMI > 95th centile [11]. The highest percentage of subjects classified as overweight was in minorities and Southerners.

There are serious medical and psychosocial consequences to excessive weight gain in children and adults. Obese adults suffer from impaired glucose tolerance, diabetes mellitus, hypercholesterolemia, hypertension, cardiovascular disease, higher rates of some forms of cancer, and inferior survival when they develop cancer [8]. Medical problems associated with obesity in adults have their beginnings in overweight children. Overweight children tend to be taller than peers, have earlier pubertal maturation and are presumed to be more mature. Excessive weight in the pediatric population is associated with hyperlipidemia, hypertension, acanthosis nigricans, diabetes and insulin resistance, hepatic steatosis, cholelithiasis, pseudotumor cerebri, sleep apnea, and orthopedic abnormalities like Blount disease and slipped capital femoral epiphysis [12]. The impact of the pandemic of childhood obesity on adult disease remains to be determined, but the appearance in children of obesity-associated illnesses typical of obese adults is a potential ominous harbinger. How obesity impacts on outcomes of pediatric cancer and other chronic diseases is unknown. The future costs to our health care system could be staggering. Between 1979 and 1991, the estimated health costs related to obesity in 6–17 years old in the US increased from $35 million to $127 million per year [13], that is more than a threefold rise.

Suggested interventional strategies have included: (1) educational tools such as the CDC website http://www.cdc.gov/nccdphp/dnpa/bmi/bmi-for-age.htm that offer training and educational modules; (2) motivational techniques to help move patient to the point of wanting change; (3) reducing sedentary behavior; (4) media promotion of lifestyle changes; and (5) development of strategies for different degrees of overweight (moderate and severe) in children and adolescents [14].

TABLE I. Percentage of Children Overweight (BMI > 95th centile)

Age (years)	NEHS 2–3, 1963–1974	NHANES I, 1971–1974	NHANES II, 1976–1980	NHANES III, 1988–1994	NHANES, 1999–2000
2–5		5.0%	5.0%	7.2%	10.4%
6–11	4.2%	4.0%	7.0%	11.3%	15.3%
12–19	4.6%	6.1%	5.0%	10.6%	15.5%

Table I depicts changes in the last 20 years of percentages of children overweight as quantified by the National Health and Nutrition Examination Surveys (NHANES) and the earlier National Health Examination Surveys (NHES) [9].

TABLE II. Prevalence of Children at Risk for Overweight (BMI > 85th centile) and Overweight (BMI > 95th centile) in USA, 1999–2000

Age in years	Group	BMI > 85th centile	BMI > 95th centile
2–5	All	20.6%	10.4%
	Female	20.4%	11.4%
	Male	20.9%	9.9%
6–11	All	30.3%	15.3%
	Female	27.8%	14.5%
	Male	32.7%	16.0%
12–19	All	30.4%	15.5%
	Female	30.2%	15.5%
	Male	30.5%	15.5%

Table II shows prevalence of overweight and obesity by age according to NHANES 1999–2000.

OBESITY AND CANCER CHEMOTHERAPY

Principles of Drug Disposition in Obese Patients

Drug dosage in obese humans has gained increasing importance, as obesity has grown more prevalent in the general population. Physiology of obesity and pharmacokinetics of drugs in obese patients have been reviewed by several authors [15–17]. This brief overview of effects of obesity on drug disposition is based on those articles.

Drug binding to blood proteins affects distribution volume of drugs, amount of free drug available for pharmacologic effect, and amount of drug free to be cleared from the body. Acidic drugs are often bound by albumin. There appears to be no change in albumin binding of drugs in obese patients. Alkaline drugs are frequently bound by α_1-acid glycoprotein. Data suggest the binding of alkaline drugs is increased in obese patients. This can result in less free drug and less acute pharmacologic effect. However, the unbound portion of the drug is excreted, so drug excretion may be slower, causing a prolonged effect.

Drugs that are highly water-soluble tend to distribute to lean body mass, suggesting that doses should be based on lean body weight rather than total body weight. This is the main factor suggesting dosage adjustment for obese patients. A smaller volume of distribution is associated with increased serum concentration, which might require

TABLE III. Prevalence of Overweight (BMI > 95th centile) by Age and Ethnicity

Age (years)	Non-Hispanic White	Non-Hispanic Black	Mexican American
2–5	10.1%	8.4%	11.1%
6–11	11.8%	19.5%	23.7%
12–19	12.7%	23.6%	23.4%

Table III shows percentages of overweight by age and ethnic group collected in NHANES 1999–2000 [9].

lower dosage for the patient. For multiple doses, drug clearance becomes a more important factor and may counteract changes in distribution volume. Distribution volume of lipid-soluble drugs in obese patients should be large, but it is difficult to predict [17]. Most drugs are not purely lipid-soluble or water-soluble, and their distribution is somewhere between the extremes.

Liver metabolism includes two main types of reactions: oxidation and conjugation. Most studies have shown that oxidative metabolism is increased or not changed in obese patients. Conjugation reactions tend to increase, with glucuronidation increased more than sulfonation. The overall effect of obesity on hepatic clearance of drugs appears to be minimal change or increased clearance.

Renal function may be unchanged or increased in obese patients [15]. Studies of excretion of renally cleared drugs in obese patients found inconsistent effects of obesity on drug clearance. Estimates of creatinine clearance using the Cockcroft–Gault equation have correlated best with actual renal function when an adjusted weight is used for the calculation [17]. A weight halfway between actual body weight and estimated ideal body weight (IBW) has worked well.

Studies of Chemotherapy and Outcomes in Obese Cancer Patients

A cohesive and comprehensive literature in this area is lacking. Only a few studies have measured pharmacokinetics of chemotherapeutic drugs in obese patients; most were not powered to show differences between obese and non-obese patients (Table IV), and all but one examined a small number of obese patients and non-obese controls. Most patients in these studies were adults. The studies usually lack correlations with clinical toxicity and efficacy. Hence the discussion of pharmacokinetics of chemotherapy drugs in obese patients reports what information is available, but cannot generalize about the pharmacology of cancer chemotherapy according to BMI and its impact on outcome.

Powis et al. [18] examined effects of obesity on pharmacokinetics of cyclophosphamide. They found reduced clearance of cyclophosphamide with no change in volume of distribution, leading to a longer half-life. Lind et al. [19] studied ifosfamide pharmacokinetics in obese patients and found no change in clearance, but larger distribution volume with prolonged half-life. Because neither examined active metabolites of the drugs or correlated their results with clinical effects of the drugs, we cannot draw definitive conclusions about the effects of obesity on the activity of cyclophosphamide.

Pharmacokinetic studies of high-dose methotrexate in one obese woman with osteosarcoma showed increased clearance and volume of distribution, yielding a half-life similar to that of normal-weight adults [20]. Doxorubicin

TABLE IV. Studies of Pharmacokinetics of Chemotherapy in Obesity (18–25)

Drug(s)	Cancer type	Obese/ controls	T 1/2	Vd	Cl	Reference
Cyclophosphamide	Breast	5/11	↑	→	↓	Powis et al. [18]
Ifosfamide	Bronchus	4/12	↑	↑	→	Lind et al. [19]
Doxorubicin	Many	4/17	↑	→	↓	Rodvold et al. [21]
Methylprednisone	No cancer	6/6	↑	→	↓	Dunn et al. [22]
Busulfan	CML; NHL; other	99/279			↑	Gibbs et al. [23]
Methotrexate	Osteosarcoma	1	→	↑	↑	Fleming et al. [20]
6-mercaptopurine	ALL	9/9	→	↑	↑	Zuccaro et al. [24]
Cyclophosphamide	Breast (SCT)	1/24		↑ AUC		De Jonge et al. [25]
Carboplatin				↑ AUC		
Thiotepa				↑ AUC		

pharmacokinetics were studied in normal, mildly obese, and obese cancer patients [21]. Doxorubicin had lower clearance, no change in volume of distribution, and longer half-life in the most obese patients, resulting in a larger area-under-the-curve and more exposure. The pharmacokinetics of doxorubicinol, an active metabolite, did not differ among patient groups.

In obese men the clearance of methylprednisolone is reduced, with no difference in volume of distribution, resulting in a prolonged half-life [22]. Obesity increased effects of methylprednisolone on cortisol, histamine, and helper T-cell responses. The authors suggest dosing methylprednisolone on the basis of IBW and perhaps with longer dosing intervals.

Gibbs et al. [23] examined oral busulfan clearance in a large group of adolescents and adults who received stem cell transplants. Clearance was higher for obese patients; however, dosing based on body surface area (BSA) or adjusted IBW corrected for the difference. Patients with chronic myeloid leukemia had higher clearance than patients with non-Hodgkin lymphoma even when dosing was based on BSA or adjusted IBW. Because the effect of interpatient variability was larger than that of obesity, the authors recommended dosing busulfan pharmacologically based on plasma levels on day 1.

Zuccaro et al. [24] studied serum concentrations of 6-mercaptopurine in 18 pediatric patients during the maintenance phase of their acute lymphoblastic leukemia (ALL) treatment. Patients that were below the 75th centile of weight/height had higher serum mercaptopurine concentrations than those above the 75th centile. The authors suggested that the more obese patients might be at risk of being underdosed, however, clinical correlations were not provided.

A conditioning regimen of cyclophosphamide, thiotepa, and carboplatin for metastatic breast cancer was studied in one obese woman [25]. Cyclophosphamide and thiotepa dosages were based on BSA calculated from actual body weight; and the carboplatin dose was calculated using the Calvert equation [26]. Thiotepa and 4-hydroxycyclophosphamide metabolites were measured along with their parent drugs, and ultrafilterable platinum was measured. Areas-under-the-curve were significantly greater than normal for all three drugs. The authors suggested that cyclophosphamide and thiotepa dosages should not be based on actual body weight in obese patients, and that use of the Cockcroft–Gault equation for this obese patient led to overestimation of creatinine clearance resulting in too high a carboplatin dose.

An entirely different group of studies describes outcomes in obese and non-obese patients. Calle et al. [27] followed over 900,000 US adults over 16 years old and found that patients who had BMI greater than 40 had increased risk of death from cancer. For women the increased risk was 62%; for men it was 52%. It is not clear whether this was due to increased incidence, worse response to treatment, or some other factor. Bastarrachea [28] studied 735 breast cancer patients who received CAF doses based on use of actual body weights to calculate surface area, and found that 10-year disease-free survival was 40% in the obese patients versus 54% in normal-weight patients. No adverse effect data were reported. The obvious question is whether they are dying from toxicity because of relative overdosing or from cancer because of altered pharmacology of antineoplastics, or comorbidities. Outcome studies of drug treatment in obese cancer patients may be affected by factors other than the drug treatment.

Several studies have suggested that chemotherapy dosages do not need to be adjusted downward in obese patients. Findlay [29] reported that in a group of over 700 premenopausal node-positive breast cancer patients, obese patients whose dosages were based on their actual weight had the same incidence of neutropenia as normal-weight patients. Obese patients dosed by IBW had approximately one-half the incidence of neutropenia. Poikonen [30] examined leukocyte counts in 340 node-positive breast cancer patients who received CMF doses based on surface area calculated by using actual body weight. Patients with high BSA or weight had higher

leukocyte nadirs than normal-weight patients. Georgiadis [31] reported on 262 small-cell lung cancer patients evenly divided between limited or extensive-stage disease. Initial drug doses were calculated based on surface area derived from actual body weight. There was no significant association between BMI and overall survival or toxicity. They concluded that their study did not justify dose reductions based on IBW.

Meyerhardt [32] reported on 3,759 patients treated for stage II or III colon carcinoma. Actual body weight at the beginning of treatment was used to calculate the BSA for dosing. Obese women, but not men, had increased overall mortality. Obese patients had less grade 3–4 leukopenia and less of any grade 3 toxicity. Meyerhardt [33] also reported on 1,688 stage II or III rectal carcinoma patients. Although there were no differences in overall mortality between men and women, obese men had a higher rate of abdominoperineal resection and of local recurrence. Obese patients had lower incidence of grade 3 or 4 leukopenia, neutropenia, and stomatitis, plus lower incidence of any grade 3 or worse toxicity. Doses for the study were calculated using BSA calculated from actual weights.

Butturini [34] examined several Children's Cancer Group ALL studies and found that children 10 years old or greater had poorer survival if they were greater than 60 kg or greater that the 95th centile for BMI. Drugs were dosed based on full body size and there was no evidence for increased drug toxicity.

Results of studies in stem cell transplant patients are different. In that setting, dosages have often been calculated based on adjusted or IBWs. Navarro [35] reported on AML patients who received autologous transplants using a conditioning regimen of busulfan and etoposide. Chemotherapy doses in obese patients were adjusted downward using weights between actual and IBWs. Survival data are not presented, but mucositis, narcotic use, alkaline phosphatase, and possibly total bilirubin were lower in obese patients. The authors suggested that obese patients might have been underdosed. All other studies in transplant suggest that obese patients experience excess toxicity. Fleming et al. [36] assessed overall survival in 322 patients who received allogeneic transplants for hematologic diseases, mostly cancer. Chemotherapy dosages were generally based on IBW. Overall survival was 20% for obese patients, compared with 35% for normal-weight patients. Relapse-related and non-relapse-related mortality were increased. The difference was not present in 67 pediatric patients, suggesting a possible difference in pediatric patients. Dickson et al. [37] studied 473 patients who received autologous transplants for hematologic malignancies. Doses were adjusted downward in obese patients. Those with low or high BMI had increased non-relapse-related mortality. Since there was no increase in relapse rates, the authors suggested that dose reductions were reasonable.

Studies of Cancer Chemotherapy in Obese Patients: Summary and Areas for Additional Research

The importance of knowing how to prescribe chemotherapy drugs in obese patients is clear. The available pharmacology studies suggest that certain drugs, diseases, or specific patients may require dosages based on an adjusted body size when the patient is obese. The outcome studies in adult solid tumor patients suggest that there may be no need to adjust chemotherapy doses downward in obese patients. Adjusting dosages down may reduce toxicity, but could decrease response rates and cures. The risk of not adjusting doses downward toward IBW is increased toxicity as shown in the majority of studies in transplant.

Data needed to understand and recommend chemotherapy doses in obese patients do not exist. There is almost no information on dosing obese children. With the exception of glucocorticoids, studies of chemotherapy pharmacokinetics have not included correlations with clinical effects. Often mortality is increased and chemotherapy toxicity is decreased in obese adult solid-tumor patients, whether dosages are reduced or not. The data for stem cell transplant patients are conflicting, but historically doses have been based on a downward-adjusted size for obese patients. An appropriate way for pediatric oncology to proceed is to retrospectively review finished studies and analyze survival and toxicities based on obesity and method of calculating dosages.

IMPACT OF OBESITY ON SURVIVAL IN CHILDHOOD ACUTE MYELOID LEUKEMIA (AML)

In 2000, there were no data concerning how childhood obesity affects survival in childhood cancer. AML is a disease with high morbidity and mortality and the disease itself is similar in children and adults. Current therapy cures AML in roughly half of young patients with de novo disease. Prolonged periods of neutropenia lead to treatment-related mortality (TRM) rates of 5%–15%. Despite this toxicity and relatively high TRM, in young patients with AML, progressive disease and relapse account for most deaths. AML provides a model for examining the impact of obesity on outcomes in patients receiving intensive and myeloablative therapy.

Children's Cancer Group study CCG-2961 is a cooperative group study based on the intensive timing chemotherapy/transplantation paradigm proven successful in CCG-2891. As previously reported [38,39] CCG-2961 involved a five-drug induction regimen in phase 1; phase 2 randomized the same five-drug regimen and a fludarabine-based combination [40]; phase 3 involved biologic randomization to marrow transplantation or chemotherapy [41]; and phase 4 interleukin 2 therapy [42,43] or standard follow-up after chemotherapy. Chemotherapy dosage was according to surface area in

children over age 3 years and per kilogram on those under 3.

CCG-2961 study committee members observed that patients who were obese seemed to have excess toxicity and mortality. These observations led to a retrospective investigation of outcomes in patients based on indices of body weight, either as percentage of IBW [44,45] in those aged 1 year or older or BMI in those over age 1 year. Overweight was defined as weight 110%–120% IBW; obese as 120%–140% IBW, morbidly obese as >140% IBW; and malnourished as <90% IBW. In all cases results based on IBW were similar to those based on BMI. BMI outcomes have recently been published [39].

IBW and outcome data were available for 770 patients of whom 103 (13.4%) were morbidly obese, 176 (22.9%) were obese or overweight, 109 (14.2%) were underweight, and 382 were normal. For most analyses, obese, overweight, and normal were grouped and classified as middleweight. Median age was 7.0 years and median white blood cell (WBC) count was 17.6×10^9/L. Morbidly obese patients were significantly older and underweight significantly younger than the middleweight group. Morbidly obese patients had significantly higher WBC counts. For reasons that are not clear, morbidly obese patients were about half as likely to have matched related donors, hence less likely to undergo marrow transplantation. There was no difference among groups with respect to randomized regimens, nor prognostically important variables of race, cytogenetics, or early response as measured by percentage of blasts in day 14 marrow. Survival and EFS were significantly lower in morbidly obese patients ($P < 0.001$ and $P = 0.009$, respectively).

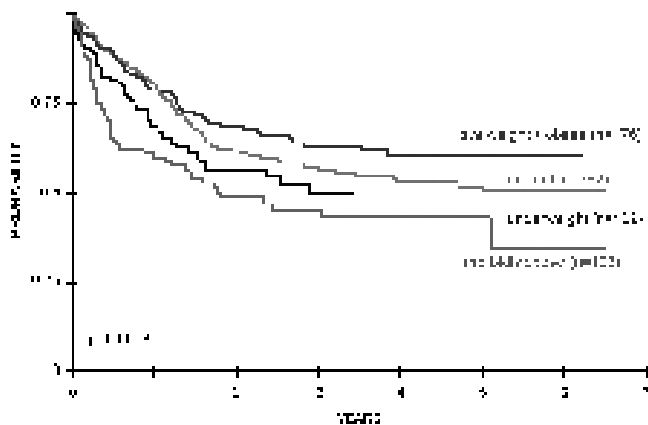Figure 1 shows survival at 3 years according to the five groups based on IBW. Compared with normal-weight patients, morbidly obese and underweight patients had significantly reduced survival, but those who were overweight or obese did not. It also shows that excess mortality occurred early in treatment. Review of the causes of death showed that most of the excess could be attributed to TRM. In morbidly obese patients, TRM after two courses of chemotherapy was 24.2% compared with 7.1% in middleweight patients ($P < 0.001$). Infection was most often cited as the cause of TRM. The finding of significantly increased TRM persisted in multivariate analysis after adjusting for age, splenomegaly, WBC, and marrow transplantation. Grade 3 and 4 toxicities, relapse rates, duration of neutropenia of survivors in induction, and time to begin consolidation were similar in the morbidly obese patients and other patients. These similarities suggest that the morbidly obese patients are not being overdosed. Interestingly, the 23% of patients who were between 110% and 140% IBW had a survival rate that was insignificantly better than that of the normal weight patients (Fig. 1).

Dosages were examined in all patients during the first two phases of therapy. Physicians were instructed to dose according to patient meters squared. Nonetheless, 4% of morbidly obese patients received less than 90% of protocol-mandated drugs, a frequency similar to the other two groups. Two died of toxicity despite dose reductions and two were long-term survivors.

CCG-2961 found that both extremes of weight for height were associated with shortened survival in pediatric patients with AML. Inferior outcomes were due to TRM in the first months of therapy.

This study shows that in addition to premature mortality from metabolic or cardiovascular disease in young adulthood morbid obesity in children and adolescents contributes to premature mortality from AML before age 21 years. These findings are in contrast to those in ALL where the obese patients experience excess relapse rather than excess TRM [34]. However, they are consistent with transplant studies adults where there was excess TRM [35–37] and with the studies involving conventional doses of chemotherapy where underdosing may be a concern [30,33]. At cancer diagnosis, it is already too late to prevent obesity, but it may be possible to prevent treatment-related deaths. As pointed out the previous section, pharmacokinetic information on chemotherapeutic agents in obese adults is scarce. Only busulfan has been examined according to indices of body weight in children. Pharmacologic studies controlling for BMI should be a priority. Assessment of nutritional and immunologic status may reveal correctable abnormalities in both morbidly obese and underweight patients. Among morbidly obese patients, control of blood glucose and blood pressure may be especially important. Also, obese patients may receive suboptimal care from nurses and doctors because of difficulties in moving patients and performing physical and radiologic assessments, as pointed out by Wiernik et al. [46].

Fig. 1. Kaplan–Meier plot of actuarial survival in morbidly obese, overweight, obese, underweight, and normal patients.

OBESITY IN SURVIVORS OF CHILDHOOD CANCER

Developing and maturing organ and endocrine systems in children and adolescents are often vulnerable to radiation therapy, chemotherapy, and surgery, leading to subsequent late effects. Exposure-specific late effects of therapy can be further modified by age at exposure, gender, or particular combinations of exposures. This concept has formed the basis for investigating late consequences of cancer therapy, with a goal of preventing or reducing risk and maximizing health of survivors [47].

An area of growing concern has been determining whether some cancer treatment exposures during childhood or adolescence increase the risk of overweight or obesity. It is particularly germane to determine if some cancer exposures lead to increased risk of obesity and how this might further influence risk of other late effects. Survivors of childhood ALL and brain tumors have been the focus of most studies that addressed potential obesity risk after cancer therapy. In the following sections, the discussion focuses on limitations in the study of obesity and fatness, the current data describing obesity in survivors, and potential mechanisms of obesity. After that discussion is a brief description of unanswered questions and future directions of research.

Limitations in the Study of Obesity and Fatness

In the general population, the most common indicator of obesity is BMI, which correlates with body fat, is inexpensive to obtain, and is relatively easy to determine retrospectively. Standardized classification of obesity is based on it [48]. Much of the literature on health implications of obesity, including an increase in all-cause mortality, are from studies that used BMI as the primary measure [49]. However, for this discussion it is important to note that there are limitations to using BMI. It does not distinguish between lean and fat tissue. Dual X-ray absorptiometry (DXA) and bioimpedance provide better estimates of percentage of body fat [50]. More importantly BMI does not provide any information on distribution of fat. Distribution of fat may be as important as total amount of fat in the development of insulin resistance [51–54]. Imaging with CT or MRI is necessary to quantify fat distribution in the abdomen and viscera. Most studies that have assessed obesity in cancer survivors were retrospective and relied upon BMI. Recently, there have been a few studies that incorporated DXA or observed survivors longitudinally through their growth and development. There are no studies in the literature that assessed body fat distribution in survivors.

Studies that evaluated obesity measures in cancer survivors also have been limited by factors commonly encountered in survivorship research. Several studies relied on small samples from single institutions, limiting generalizability of findings and ability to analyze associa-tion of obesity with various treatment exposures. Some studies lack a comparison or control group. With the pandemic of obesity in the general population, a study without a comparison group for perspective may overstate the risk associated with cancer therapy. Finally, and perhaps most importantly, most studies have been cross-sectional and report on BMI at completion of therapy, 2–4 years after therapy, or at attainment of final height. The number of studies that have included survivors, who matured into their young adult years, are limited.

Current Data Describing Obesity in Survivors of Childhood Cancer

Zee and Chen [54] at St. Jude Children's Research Hospital provided the first report of potential association between obesity and ALL therapy in 1986 when they reported excess weight gain in 414 ALL survivors [54]. Since then several studies have reported on BMI in ALL survivors [55–67] and provide growing preponderance of evidence of association of ALL therapy with obesity. Depending on obesity definition and timing of measurement, the reported prevalence of obesity in ALL survivors ranges from 11%–57% (Table V).

A recent Childhood Cancer Survivor Study (CCSS) reported on 1,765 young adult ($\geq$18 years old) survivors of childhood ALL and a comparison group of 2,565 siblings of childhood cancer survivors [66]. Exposure to doses $\geq$20 Gy of cranial radiotherapy (CRT) was associated with an increased likelihood of obesity. Compared with siblings of cancer survivors, female ALL survivors who had been treated with CRT $\geq$ 20 Gy were 2.59 times as likely to be obese (95% CI, 1.88–3.55). Male survivors with the same exposure were 1.86 times as likely to be obese (95% CI, 1.33–2.57) as the same-sex comparison group. Further, it was noted that age at treatment modified risk, particularly in females. Those diagnosed at 0–4 years old and treated with CRT $\geq$ 20 Gy were 3.81 times as likely to be obese (95% CI, 2.34–5.99) as siblings. In this subgroup, of those who were 20–29 years of age at study, 31% were overweight and 24% were obese (55% either overweight or obese). In contrast, in females 20–29 years of age participating in the NHANES III, 19% were overweight and 15% were obese (34% either overweight or obese) [68].

Convincing evidence is still lacking of increased obesity risk in survivors treated with chemotherapy alone or with lower doses of CRT. Studies that have suggested these two populations are at risk of obesity have been limited by small samples, lack of comparison groups, or limited duration of follow-up [58,60,61]. The CCSS study included 421 survivors who were treated with chemotherapy only and 503 who were treated with chemotherapy combined with CRT 10–19 Gy [66]. All subjects were 18 years or older at time of study. Interestingly, ALL

TABLE V. Prevalence of Obesity Following Therapy for Acute Lymphoblastic Leukemia (ALL)

Study	Treatment exposure			Age at study	Obesity definition	Comparison group	Prevalence
	Chemo only	10–19 Gy CRT	≥20 Gy CRT				
Odame et al. [56]	—	40	—	2 years post DX 4 years post DX	BMI-SDS > 85th centile	Other survivors	40%
Van Dongen-Melman et al. [58]	62	—	52	Complete RX	BMI-SDS > 90th centile	No	24%
Mayer et al. [62]	14	25	–	4 years post DX 14 years of age	BMI-SDS > 2 SD	No	38%
Nysom et al. [61]	56	22	17	DX; Off RX (16 years of age)	BMI-SDS ≥ 90th centile	Population controls	26%
Schell et al. [55]	—	—	91	Final height	BMI ≥ 24	No	38%
Didi et al. [57]	—	50	64	Final height	BMI-SDS > 85th centile	No	46%
Shaw et al. [63]	—	15	18	Final height	BMI-SDS > 85th centile	No	56%
Craig et al. [60]	85	118	95	Final height	BMI-SDS > 2 SD	No	11%
Sklar et al. [63]	38	35	53	Complete RX (final height)	BMI-SDS ≥ 85th centile	No	30%
Birkebaek and Clausen [59]	11	—	22	DX (final height)	BMI-SDS > 90th centile	No	36%
Oeffinger et al. [65]	16	—	10	21 years old	BMI ≥ 30	No	31%
Oeffinger et al. [66]	421	503	841	≥18 years old (mean = 24.1)	BMI 25–29 (overweight ≥ 30 obese)	Siblings of survivors (N = 2,565)	28% overweight, 17% obese, 45% both

Chemo, chemotherapy; CRT, cranial radiotherapy; DX, diagnosis; RX, cancer therapy; BMI, body mass index; SDS, standard deviation score.

survivors who were treated with CRT 10–19 Gy or with chemotherapy only had no increased risk of overweight or obesity.

For many years, the risk of obesity has been recognized after diagnosis and treatment of childhood craniopharyngioma [69–71]. Survivors of this brain tumor, which generally involves the pituitary stalk and hypothalamus, experience an array of endocrinopathies related to damage of the hypothalamic-pituitary axis caused by the tumor, surgery, or subsequent hypothalamic radiation. Lustig et al. [69] studied risk factors of obesity in 148 brain tumor survivors and found that hypothalamic damage from tumor, surgery, or radiation was the primary cause. In a study of 921 brain tumor survivors in the CCSS (which did not include craniopharyngioma survivors), Gurney et al. [72] found that only females treated with radiation were at risk of obesity. As with the ALL survivors, females treated at a younger age were at highest risk of obesity.

Potential Mechanisms of Obesity After Cancer Therapy

Though there are several potential mechanisms that may contribute to risk of obesity, the primary one appears to be injury to the hypothalamic-pituitary axis. The classic example is the craniopharyngiomas survivor, who can have, as noted above, damage to this area secondary to tumor, surgery, or radiation. In ALL and other brain tumor survivors, the one exposure that has been repeatedly associated with obesity is cranial irradiation. It has been postulated that CRT during this vulnerable development period leads to leptin-insensitivity and/or growth hormone deficiency (GHD), resulting in obesity. Supporting the possible role of leptin-receptor insensitivity in radiation-associated obesity, Brennan et al. [73] reported that leptin levels were significantly higher, with an increase in leptin per unit of fat mass, in 32 ALL survivors who had been treated with 18–25 Gy CRT compared with 35 age- and BMI-matched controls. Differences were most marked for those with GHD and to a lesser degree those with insufficient growth hormone peaks. Survivors with normal growth hormone stimulation did not have raised leptin levels or a difference in leptin to fat mass compared with controls. Radiation-associated obesity also may be mediated through alterations in growth hormone secretion. GHD in adulthood, regardless of etiology, is associated with obesity [74]. A significant proportion of adult survivors of childhood ALL who were treated with CRT are growth hormone deficient [75]. In an analysis of body fat determined by DXA in 95 survivors of childhood ALL, Nysom et al. [61] found a higher percentage of fat related to GHD in those who had been treated with CRT. It is likely that radiation damage to the more radiosensitive hypothalamus [76,77] results in both leptin-receptor insensitivity and varying degrees of GH insufficiency.

Other therapeutic exposures (e.g., corticosteroids) or mechanisms (e.g., early adiposity rebound, physical inactivity) have also received attention. Energy intake is significantly increased in children on maintenance therapy for ALL and believed related to corticosteroid use [78]. This excess in energy intake, if not balanced by an increase

in energy expenditure, will lead to increased body fat. Reilly et al. [79] suggested that treatment of ALL may cause a premature adiposity rebound resulting in increased risk of obesity. Several studies reported reduced energy expenditure in ALL survivors, specifically a decrease in habitual physical activity [62,80,81].

Unanswered Questions and Future Directions

The one exposure for which there is a preponderance of evidence supporting association with obesity in adulthood is CRT ≥ 20 Gy. Thus, for the many leukemia and brain tumor survivors treated with this exposure, it is important to identify methods to successfully treat obesity, limit excessive weight gain, and evaluate for comorbid health conditions, such as insulin resistance that often accompany obesity. What is unanswered is whether or not ALL survivors treated with lower dose CRT or chemotherapy only face an increased risk of becoming obese adults. Perhaps of equal importance is determining if the location of fat deposition is different than the general population, and whether or not this will lead to an increased risk of metabolic syndrome and cardiovascular disease.

One of the authors (K.C.O.) is currently leading a 4-year NCI-supported study assessing fatness in 180 young adult survivors of childhood ALL, using several measures including BMI, waist circumference, DXA for percent body fat, and CT for abdominal fat content and distribution. This study will also test an intervention intended to increase sustainable levels of physical activity in this population. Similar studies are in progress in other parts of North America and Europe and will provide important information on risks of childhood cancer survivors.

DISCUSSION

This review highlights the general pediatric problem of obesity that is pandemic and its relevance to pediatric oncology patients. In studying the obesity problem, obesity needs to be consistently defined and appropriately assessed. Currently BMI is the accepted index above 2 years old. Changes in BMI should be evaluated prospectively. Pediatric oncology health care providers need to be cognizant of the problem of obesity, the potential impact of obesity on cancer incidence, treatment, and long-term morbidity.

An immediate concern is the impact of this host factor on pharmacokinetics of treatment. Our current dosing system based on square meter-age or per kilogram is crude and does not take into account inter- and intrapatient variability of pharmacokinetics and pharmacogenetics, and how that they may affect the pharmacodynamics and effectiveness of treatment for specific malignancies. The appropriate prescription of drugs is considered fundamental in treatment, and obesity adds to the problem of what is appropriate dosage. Inappropriately dosing patients could explain why AML and ALL who are obese appear to have poorer prognoses. However, this is an intuitive response. We know nothing about the interaction of obesity genes and oncogenes and how our therapeutics may affect them. The biology of obesity is a highly complex interaction of genes, hormones, and signals of adipose development. Their interaction in patients with cancer is poorly understood. The complexity of genetics and hormonal interaction is daunting but warrants exploration within cooperative clinical trials.

Survivors of pediatric malignancies have many long-term sequelae that affect their quality of life, and obesity further impinges on their quality of life and self esteem. How obesity affects other long-term sequelae of cancer requires study. There are many obvious examples. Does obesity increase risk for delayed cardiomyopathy due to anthracyclines? Does obesity add to the risk of hypertension in patients with Wilms tumors? Does it enhance the hyper filtration syndrome? Is obesity a risk factor for the development of second malignancies? The challenge for clinical investigators will be to develop interventional strategies that reduce obesity prevalence and associated morbidity. The obvious interventions of improving physical activity, nutritional guidance, and behavioral modifications need to be evaluated for utility. It may be fundamental that genes associated with obesity do not allow expected responses to interventional changes. Proactive interventions during treatment require attention to any interactions with cancer and its treatment. The Nutritional Committee of COG believes that nutrition evaluation on and off treatment is important in relationship to obesity and the effect of nutritional status on cancer. The following are areas of potential study: review of obesity prevalence and correlations with outcome and treatment in specific diseases; prospective assessment of obesity using objective methods of body mass composition; investigation of the pharmacology of chemotherapy in obese patients; investigation of biology of obesity in oncology patients, for example leptins and other mediators of obesity. By asking well-thought questions within the cooperative group mechanism we can answer the questions of obesity affecting our pediatric oncology patients.

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