Toxic effect of chemotherapy dosing using actual body weight in obese versus normal-weight patients: a systematic review and meta-analysis

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Background: Many oncologists reduce chemotherapy doses in obese patients due to fear of excess toxic effect from very large weight-based calculations. While recent guidelines advise against this practice, quantitative summarization of the supporting evidence is not available.

Materials and methods: We systematically identified studies that compared toxic effect or survival outcomes between obese and normal-weight adults receiving chemotherapy dosed by actual body weight (ABW). We pooled odds ratios (OR) and 95% confidence intervals (CI) using random-effects models.

Results: Of 5490 records screened, 12 studies representing 9314 relevant patients met inclusion criteria. The large majority of reported toxic effect and survival outcomes did not statistically differ between obese and normal-weight patients.
subjects. Exceptions included five studies in which one or more toxic effect or survival outcomes statistically favored obese patients, and one study that statistically favored normal-weight patients. Pooling usable data, rates of toxic effects were similar or lower in obese patients (grade 3/4 hematologic toxic effect: OR 0.73, CI 0.55–0.98, 4 studies; grade 3/4 nonhematologic toxic effect: OR 0.98, CI 0.76–1.26, 3 subgroups; any grade 3/4 toxic effect: OR 0.75, CI 0.65–0.87, three studies).

Conclusions: Obese patients receiving chemotherapy based on ABW experience similar or lower rates of toxic effects compared with normal-weight patients, and survival outcomes do not differ.

Key words: chemotherapy, dosing, obesity, survival, toxic effect

introduction

With approximately one-third of Americans now obese (as defined by a body mass index, or BMI, ≥30 kg/m²) [1], determining appropriate methods for dosing chemotherapy in obese patients is important for ensuring safe and effective cancer care for an increasingly large segment of the population. Traditionally, dosing recommendations for chemotherapy agents are determined during phase I and II clinical trials in which researchers, aiming to maximize antineoplastic effect, gradually increase the dose until they reach a level at which an unacceptable toxic effect occurs, then return to the dose just preceding this level—the so-called maximal tolerated dose [2, 3]. Since the 1950’s, researchers have used body surface area (BSA), a number determined by a person’s height and actual body weight (ABW), to translate dose levels identified in animal studies to doses appropriate for humans in phase I trials [4–6]. The use of BSA for dosing carries over to phase II and III trials and ultimately to clinical practice.

Problems arise when patients are obese, as dose calculations based on BSA can be very high. Many practitioners, fearing excess toxic effects with such large doses, respond by reducing the doses of chemotherapy given to obese patients. Clinical practice varies significantly, both in terms of whether doses are reduced and, if so, how this is done [7, 8]. Some practitioners use ideal body weight (IBW), rather than ABW, when calculating BSA for obese patients; a morbidly obese patient dosed in this way could receive 25% less chemotherapy than a similar patient seen by an oncologist who doses by ABW [9].

Many practitioners calculate BSA based on ABW, but then arbitrarily reduce the dose in obese patients; up to 37% of severely obese patients receive dose reductions of at least 10% during the first cycle of chemotherapy [7, 10–12]. Finally, some practitioners ‘cap’ chemotherapy doses in obese patients, either by using a maximal BSA of 2.0 m² or by capping the absolute dose of a drug given [12, 13].

This tendency toward dose reduction leads to another problem. Multiple individual studies have shown that obese patients, compared with normal-weight patients, often experience less myelosuppression (and other toxic effects) while undergoing chemotherapy [14–16]. While at first glance this sounds like a good thing, evidence suggests that chemotherapy-induced neutropenia predicts increased survival [17–19]. As such, less toxic effect may translate into worse outcomes. In fact, obesity has been associated with poorer survival in many cancers, including breast, colon, ovarian, and prostate cancers [20–28]. While this poorer survival is multifactorial, there is some evidence to suggest that chemotherapy underdosing in obese patients may be contributing to these worse outcomes.

Regardless of body weight, reducing the dose intensity of chemotherapy has been shown to negatively impact survival in multiple cancer types [29–34].

To better define the risks and benefits of giving full-dose chemotherapy to obese patients, we conducted a systematic review and meta-analyses of studies comparing toxic effect and survival in obese and normal-weight adult patients when both groups received chemotherapy dosed using ABW without dose reductions.

materials and methods

We wrote a protocol outlining our planned approach to identifying and selecting studies for the review and used standard methodology to analyze and report our findings [35, 36].

search strategy

With the assistance of a professional research librarian, we searched Medline, the Cochrane Library, and ISI Web of Science from their inception through 30 March 2012. Search terms included ‘body weight’, ‘cancer’, ‘chemotherapy’, and ‘dosing.’ Searches were limited to articles examining ‘humans.’ All languages were included, and one publication in Japanese was translated by a native speaker [37]. We searched ClinicalTrials.gov (last accessed July 17, 2013) to identify ongoing or unpublished trials. We manually reviewed the reference lists of studies that met inclusion criteria and the subsequent studies that cited them (as identified by Web of Science through 18 May 2012). See supplementary Figure S1, available at Annals of Oncology online for detailed search strategies.

study selection

Two reviewers independently screened each unique record identified by the searches, first by title and abstract, then by full-text when necessary. To be eligible: (i) the population consisted of adults 18 years of age or older, with cancer of any type, receiving chemotherapy based on ABW. Studies needed to either explicitly state that all subjects received full-dose chemotherapy (allowing a maximum of 15% variability from ABW) or provide individual data points that allowed us to include patients who met these criteria; (ii) the findings were reported according to obese (BMI ≥30 kg/m²) and normal-weight (BMI 18.5–24.9 kg/m²) categories, as defined by the 1995 WHO criteria. Studies that defined normal weight equal to BMI ≤25 kg/m² were also accepted, and if a study was conducted before 1995, the conventional definitions at that time were accepted (obesity equals BMI ≥27.3 kg/m² and normal
weight equals BMI <27.3 kg/m²); (iii) the design had a concomitant control; (iv) the subjects were followed for a minimum of one chemotherapy cycle; and (v) the study reported at least one of our prespecified outcomes of interest. Studies in which patients received capped doses or <85% of full-dose chemotherapy by ABW were included only if a patient subgroup receiving full-dose chemotherapy was independently presented. Studies linking obesity to a particular toxic effect only through multivariate analysis of risk factors for the toxic effect were excluded.

**Data collection and quality assessment**

After isolating the eligible studies, two independent reviewers used a predefined data collection form to collect information related to design, setting, population, exposure, comparison, and outcomes. Methodological quality was assessed using 12 of the 27 items from a checklist developed by Downs and Black for evaluating the methodological quality of both randomized and nonrandomized studies [38]. See supplementary Table S2, available at Annals of Oncology online for tool and results. Missing data that were pertinent to inclusion or exclusion of studies were sought from authors by email request. Discrepancies in study selection, data collection, and quality assessment were resolved via discussion.

**Data synthesis and analysis**

**Outcomes.** We prespecified the rate of grade 3/4 hematologic toxic effect, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (any version) [39], as the primary outcome because it encompasses the most common toxic effect-related reasons for reduction or delay in chemotherapy dosing. Prespecified secondary toxic effect outcomes included nadirs of platelets, hemoglobin, and/or leukocytes; rate of febrile neutropenia; rate of grade 3/4 nonhematologic toxic effects, and rate of any grade 3/4 toxic effect. We also explored overall survival and disease-free survival, with the hypothesis that if obese patients were able to tolerate full weight-based chemotherapy, their survival might be more comparable to normal-weight patients receiving the same chemotherapy for the same cancer.

**Qualitative analysis.** To provide a complete summarization of all available data, we collected all findings relevant to our prespecified outcomes, regardless of analysis method or reporting format. For each reported outcome, we made a qualitative determination of which group had lower toxic effect or longer survival; we reported ‘neither’ if a difference was not statistically significant between groups (P-value >0.05 or explicitly stated by the authors). When P-values assessing the difference between the obese and normal-weight groups were not provided, we accepted the P-value for the test of trend across all BMI categories from normal weight to obese, or the P-value assessing the correlation between the outcome and BMI as a continuous variable. In order to increase the depth of the information provided, we also included the quantitative result and measure of significances as provided by the primary studies.

**Meta-analysis.** When more than one study or study subgroup provided adequate data for quantitative pooling of a prespecified dichotomous outcome, we calculated odds ratios using random-effects models and RevMan 5.1 analysis software (Cochrane Collaboration, Copenhagen, Denmark). For the primary outcome, some studies reported the combined rate of any grade 3/4 hematologic toxic effect while other studies reported rates of individual grade 3/4 cytopenias (thrombocytopenia, anemia, leukopenia, neutropenia). Based on a previously demonstrated correlation between leukopenia and survival [19], grade 3/4 leukopenia was selected as the most important component of hematologic toxic effect and used to represent grade 3/4 hematologic toxic effect in the absence of an overall rate.

We assessed for heterogeneity among the findings contributing to each qualitatively summarized outcome by looking for apparent outliers. Heterogeneity among the findings contributing to each quantitatively pooled summary estimate was assessed using RevMan. We considered excessive heterogeneity to be present if the test of heterogeneity yielded a P-value <0.10 or an I²-value >50%. In cases of heterogeneity, we attempted to identify possible explanations based on differences in methodological quality, patient characteristics, chemotherapy regimens, and/or outcome definitions. If heterogeneity could not be resolved, a quantitative summary estimate was not calculated.

To assess for reporting and publication bias, the findings were arranged by study size and informally evaluated for any association with effect size for the primary outcome. In addition, subset analyses were carried out eliminating first the smaller and then the larger studies.

When more than one study contributed to a quantitative summary estimate, we evaluated the impact of each element of the methodological quality assessment tool by comparing the magnitude and significance of the overall summary estimate (including all studies that reported usable data for the outcome) to a restricted summary estimate (including only those studies that scored ‘present’ for that methodological quality element).

**Results**

**Search results and study characteristics**

Combining the potentially eligible studies identified by each search approach resulted in 5490 unique records (Figure 1), of which 12 met all inclusion criteria (Table 1) [22, 40–49]. The studies involved a total of 9314 obese and normal-weight patients. While the majority of subjects had colorectal cancer (55%) or breast cancer (29%), 13 different types of cancer were represented. Similarly, while most patients received 5-FU or capetibamine in an adjuvant setting, the studies used 21 different chemotherapy agents, representing the major classes of antineoplastic drugs. Two studies included combined chemotherapy and radiation [14, 43]; one evaluated autologous stem cell transplantation among patients with acute myelogenous leukemia [42]. Only one of the included studies commented on the use of G-CSF, which was not allowed until grade 4 leukopenia had already appeared [44]. All studies were observational in design and most used data from previously conducted randomized trials or patients on chemotherapy.
leukopenia among obese subjects [22, 43], and one study that patients undergoing stem cell transplantation [42].

the recovery of leukocytes) occurred in the Meloni study evaluating among obese subjects [43]. The one reported a significantly lower rate of grade 3/4 hematologic toxic effect. Quantitative pooling of the four studies [22, 43, 46, 47] (six cancer-chemotherapy combinations) that specifically reported rates of grade 3/4 hematologic toxic effect or leukopenia showed that when chemotherapy was dosed by ABW, toxic effect was significantly lower in obese patients than in normal-weight patients [OR 0.73, 95% confidence interval (CI) 0.55–0.98; \(I^2 = 41\%\)] (Figure 2). Sensitivity analyses based on each domain of the methodological quality assessment did not meaningfully affect the magnitude or significance of the overall summary estimate and no relationship was detected between the sizes of the studies and their reported effect sizes.

cell line nadirs. While two studies [14, 45], including one with six chemotherapy subgroups, reported leukocyte nadirs, there was unacceptable heterogeneity among the contributing findings \((P < 0.00001, I^2 = 88\%)\) to calculate a meaningful pooled summary estimate. Poikonen et al. [45] demonstrated less toxic effect (higher leukocyte nadirs) among obese patients than normal-weight patients. While the Georgiadis study found no statistically significant differences in leukocyte nadirs for any of the six subgroups, the results varied significantly across the subgroups [14]. A third study (Miya et al.) reported percent-change in white blood cell count without giving baseline or nadir numbers [44]; an attempt to obtain the original data was unsuccessful. Based on reported correlation analyses, BMI appeared to be inversely correlated with the degree of leukocytopenia \((P = 0.068)\). Platelet nadirs were reported in only one study (Georgiadis), which found no difference for any of the six subgroups [14]. No study reported hemoglobin nadirs.

nonhematologic toxic effect

Eight studies, including 14 cancer-chemotherapy combinations, reported on one or more nonhematologic toxic effects. As detailed in Table 2, there were no statistically significant differences between the obese and normal-weight groups for the majority of reported outcomes. Exceptions included lower stomatitis rates for obese subjects in the Meyerhardt Intergroup Trial 0114 study [43] and lower rates of grade 3/4 nonhematologic toxic effects among obese patients in the Farker study, which found BMI was inversely correlated with grade 3/4 nonhematologic toxic effects \((r = -0.575, P = 0.02)\) [41]. The two findings that showed significantly less toxic effect in normal-weight patients occurred in the Meloni study assessing patients undergoing autologous stem cell transplantation [42] and the Jones study assessing patients receiving CHOP-based therapy for non-Hodgkin’s lymphoma [47], both of which found higher rates of infection among obese subjects. Quantitative pooling of the three subgroups of the Rosner study that reported usable data [46] found no difference in grade 3/4 nonhematologic toxic effect between obese and normal-weight patients \((OR 0.98, 95\% CI 0.76–1.26; I^2 = 0\%)\) (Figure 3).

any toxic effect

Five studies reported a finding aimed at capturing both hematologic and nonhematologic toxic effects. As detailed in Table 2, two studies showed less toxic effect in obese patients [22, 43], one showed less in normal-weight patients [47], and

overall hematologic toxic effect.

Eight studies, including 15 discrete cancer-chemotherapy combinations, reported on hematologic toxic effect, either as rates of any grade 3/4 hematologic toxic effect, rates of one or more separate grade 3/4 cytopenias (thrombocytopenia, anemia, leukopenia, and/or neutropenia), rates of febrile neutropenia, or as mean/median change in platelets [44] and one for leukocyte nadir [45]), two studies that found significantly lower rates of grade 3/4 leukopenia among obese subjects [22, 43], and one study that reported a significantly lower rate of grade 3/4 neutropenia among obese subjects [43]. The one finding that significantly favored normal-weight patients (based on median days to recovery of leukocytes) occurred in the Meloni study evaluating patients undergoing stem cell transplantation [42].
Table 1. Studies examining toxicity of chemotherapy dosing using actual body weight in obese versus normal-weight patients

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Design (source)</th>
<th>Country/years of treatment</th>
<th>Study population cancer type</th>
<th>Chemotherapy</th>
<th>BMI obese cohort (kg/m²) (number)</th>
<th>BMI normal-weight cohort (kg/m²) (number)</th>
<th>Dosing</th>
<th>Quality score (out of 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgiadis (1995)</td>
<td>Retrospective cohort (three protocols)</td>
<td>USA/1977–1993</td>
<td>Small-cell lung cancer</td>
<td>CMC or etoposide/cisplatin/etoposide/cisplatin/etoposide/cisplatin</td>
<td>≥27.8 (males) (n = 71) (&lt;27.3 (females) (n = 191)</td>
<td>ABW for 100% of patients</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Rosner (1996)</td>
<td>Nested cohort (RCT)</td>
<td>USA/1985–1991</td>
<td>Women with stage II breast cancer</td>
<td>Cyclophosphamide, doxorubicin, and fluorouracil</td>
<td>≥27.3 (n = 408) (&lt;27.3 (females) (n = 818)</td>
<td>ABW (all drugs within 5% of ABW dose)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Poikonen (2001)</td>
<td>Retrospective cohort</td>
<td>Finland/1987–1993</td>
<td>Women with pT1–4 node-positive breast cancer without distant metastases</td>
<td>Cyclophosphamide, methotrexate, fluorouracil</td>
<td>≥30* (n = 25) 18.5–25* (n = 175)</td>
<td>ABW (all patients received &gt;85% of dose)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Meloni (2001)</td>
<td>Retrospective cohort (consecutive subjects)</td>
<td>Italy/1981–1999</td>
<td>Patients with acute myelogenous leukemia who underwent autologous SCT</td>
<td>Busulphan/cyclophosphamide conditioning</td>
<td>≥27.8 (males) (n = 9) (&lt;27.8 (females) (n = 37)</td>
<td>NR</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Meyerhardt (2003)</td>
<td>Nested cohort (RCT)</td>
<td>USA/1988–1992</td>
<td>Stage II–III colon cancer</td>
<td>Leucovorin/levamisole/5-FU</td>
<td>≥30 (n = 600) 21.0–24.9 (n = 1166)</td>
<td>ABW for 95.1% of obese and 97.1% of comparison</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Meyerhardt (2004)</td>
<td>Nested cohort (RCT)</td>
<td>USA &amp; Canada/1990–1992</td>
<td>Stage II–III rectal cancer</td>
<td>Leucovorin/levamisole/5-FU</td>
<td>≥30 (n = 360) 20.0–24.9 (n = 611)</td>
<td>ABW for 97.7% of obese and 98.0% of comparison</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Colleoni (2005)</td>
<td>Retrospective cohort (four RCTs)</td>
<td>International/1978–1993</td>
<td>Premenopausal women with node-positive breast cancer</td>
<td>Cyclophosphamide, methotrexate, fluorouracil</td>
<td>≥30 (n = 152) &lt;25 (n = 1079)</td>
<td>ABW (all patients received &gt;85% of dose)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Barrett (2008)</td>
<td>Nested case-control (RCT)</td>
<td>International/1998–2000</td>
<td>Ovarian cancer</td>
<td>Docetaxel/carboplatin or paclitaxel–carboplatin</td>
<td>≥30 (n = 129) 18.5–24.9 (n = 582)</td>
<td>ABW for 91% of obese and 92% of comparison</td>
<td>9</td>
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<tr>
<td>Jones (2010)</td>
<td>Retrospective cohort (eight protocols)</td>
<td>USA/1988–2001</td>
<td>Intermediate-grade B-cell non-Hodgkin lymphoma</td>
<td>One of seven different chemo regimens (most with CHOP backbone)</td>
<td>≥30 (n = 166) 18.5–24.9 (n = 278)</td>
<td>ABW (94.6% of planned dose given overall)</td>
<td>12</td>
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<tr>
<td>Chambers (2012)</td>
<td>Nested cohort (three trials)</td>
<td>United Kingdom/2000–2003</td>
<td>Metastatic colorectal cancer</td>
<td>5-FU or capecitabine with oxaliplatin or irinotecan</td>
<td>≥30 (n = 404) &lt;25 (n = 2070)</td>
<td>ABW for 100% of patients analyzed</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

All studies involved follow-up for ≥1 cycle of chemotherapy.
*Individual data abstracted from graph.
ABW, actual body weight; BMI, body mass index; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CMC, cyclophosphamide, methotrexate, lomustine; 5-FU, 5-fluouracil; NR, not reported; SCT, stem cell transplant.
### Table 2. Summary of reported toxicity and survival outcomes

<table>
<thead>
<tr>
<th>Study Author, Year</th>
<th>Chemotherapy</th>
<th>Measure</th>
<th>Grade 3/4 Thrombocytopenia</th>
<th>Anemia</th>
<th>Leukopenia</th>
<th>Neutropenia</th>
<th>Fibrinogen</th>
<th>Toxicity</th>
<th>Measure</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgiadis, 1995</td>
<td>1: CAF 300/30/300</td>
<td>Mean nadir ($\times$10^9 cells)</td>
<td>&quot;</td>
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<td></td>
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<td>obese versus normal; P from three-level KW, all three analyses provided NS findings</td>
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<tr>
<td>2: CAF 400/400</td>
<td></td>
<td>3.9% versus 4.6%, P = 0.81</td>
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<tr>
<td>3: CAF 600/600/600</td>
<td></td>
<td>47% versus 51%, P = 0.51</td>
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<tr>
<td>Miya, 1997</td>
<td>Capilatin + etoposide</td>
<td>Simple linear regression</td>
<td>&quot;</td>
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</tr>
<tr>
<td>Poelksen, 2001</td>
<td>CAF 400/400</td>
<td>Mean nadir ($\times$10^9 cells); obese versus normal; Spearman correlation coefficient</td>
<td>&quot;</td>
<td>&quot;</td>
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<td>&quot;</td>
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<tr>
<td>Meloni, 2001</td>
<td>Autologous stem cell transplantation</td>
<td>Median days to recovery; obese versus none obese, log-rank P</td>
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</table>

**Nonhematologic toxicity**

- **Any toxicity**
- **Survival**

**Hematologic toxicity**

- **Thrombocytopenia**
- **Anemia**
- **Leukopenia**
- **Neutropenia**

- **Fibrinogen**

**Chemotherapy Measure**

- **Hematologic**
- **Nonhematologic**

**Any toxicity**

- **Failure-free survival, % obese versus normal, adjusted HR, unadjusted P-value**
- **Disease-free**
- **Overall**

**Survival Analyses**

- **Median survival**
- **Probability DFS/OS at**

- **Continued**
When *P*-values assessing the difference between the obese and normal-weight groups were not provided, we accepted the *P*-value for the test of trend across all BMI categories from normal weight to obese, or the *P*-value assessing the correlation between the outcome and BMI as a continuous variable.

*Patients not medically fit for random selection of chemotherapy.

**BMI, body mass index; CAF, cyclophosphamide, doxorubicin, and 5-fluorouracil; CALGB, Cancer and Leukemia Group B; cis, cisplatin; CMC, cyclophosphamide, methotrexate, lomustine; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DFS, disease-free survival; ER, estrogen receptor; 5-FU, 5-fluorouracil; IBCSG, International Breast Cancer Study Group; INT, Intergroup trial; KM, Kaplan–Meier; KW, Kruskal–Wallis test; M-H, Mantel–Haenszel test; NR, not reported; NS, nonsignificant; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; SCOTROC, Scottish Randomized Trial in Ovarian Cancer; WBC, white blood count.
two found no statistically significant differences between the obese and normal-weight groups [14, 49]. While four studies [22, 43, 47, 49] including six cancer-chemotherapy combinations provided usable data for quantitative pooling of any grade 3/4 toxic effect, the test for heterogeneity confirmed significant variability among the findings (\( P < 0.00001, I^2 = 95\% \)). The heterogeneity was readily attributable to the study by Jones et al. [47], and review of the findings revealed that the study’s differing result appeared to be driven largely by higher infection rates among obese patients (none of the other grade 3/4 toxic effects were statistically different). After removing the outlying study, heterogeneity among the remaining three studies [22, 43, 49] (including five cancer-chemotherapy combinations) disappeared (\( I^2 = 0\% \), \( P = 0.89 \)) and the summary estimate indicated that when chemotherapy was dosed according to ABW, any grade 3/4 toxic effect was lower in obese patients than in normal-weight patients (OR 0.75, 95% CI 0.65–0.87) (Figure 4).

**survival**

Among eight studies comparing overall survival in obese and normal-weight patients [14, 22, 40, 42, 43, 45, 47, 48], the majority reported no statistically significant difference between the groups. Exceptions included the study of autologous stem cell transplant patients (Meloni), which showed longer survival in normal-weight subjects [42], and the Jones study, which showed longer survival in obese patients [47]. Among eight studies comparing progression-free survival in obese and normal-weight patients [22, 40, 42, 43, 45–48], six reported no statistically significant difference between the groups.

**discussion**

Based on currently available evidence, we found that when chemotherapy was dosed by ABW, pooled rates of both grade 3/4 hematologic toxic effects and any grade 3/4 toxic effect were significantly lower in obese versus normal-weight patients. In addition, qualitative summarization of the 10 studies that reported at least one toxic effect outcome demonstrated that nearly every finding either showed less toxic effect in the obese group or found no statistically significant difference between obese and normal-weight subjects. In the single outlier study with more overall toxic effect in obese patients in the quantitative analysis [47], the difference was largely driven by increased rates of infection, an outcome that may be more likely attributable to other factors that commonly accompany obesity, such as diabetes, than to chemotherapy dosing. The single study that consistently showed less toxic effect in normal-weight patients in qualitative summaries was also the only study evaluating bone marrow transplantation [42], and arguably should not have been included, as our primary outcome of grade 3/4 hematologic toxic effects may be less relevant in transplant patients. None of the studies reported a statistically significant difference in survival outcomes, though point estimates trended toward longer survivals for normal-weight patients more often than for obese patients. Whether providing...
full ABW-dosing to both obese and normal-weight patients narrowed the previously documented differences in survival cannot be answered by our review, but the absence of a clear difference between groups is encouraging. Overall, our findings provide strong support for providing full weight-based chemotherapy doses to obese patients with solid tumors, without fearing excess toxic effects.

Like our review, a previous analysis by Hunter et al. [50] and recent consensus guidelines by Griggs et al. [51] concluded that obese patients receiving full-dose chemotherapy do not experience more myelosuppression and other toxic effects than normal-weight patients; however, neither was able to quantitatively estimate the magnitude and significance of the differences as we have. Despite our strict inclusion criteria, our systematic review also incorporates results from several additional studies not included in the prior reviews [41, 42, 44, 47, 49]. Our findings complement the expert guidelines by providing both qualitative and quantitative summaries to support the recommendations.

It is disappointing that, among the thousands of studies that have evaluated the effects of ABW-dosed chemotherapy in cancer patients, only 12 reported outcomes according to body weight. Nonetheless, our review reflects the experiences of more than 9300 patients, with 13 different types of cancer and receiving 21 different chemotherapeutic agents. While most of the patients represented in the studies had colorectal or breast cancer, it is unlikely that underlying cancer type affected the toxic effects of chemotherapy. The majority of the patients in the included studies received 5-FU or capecitabine in the adjuvant setting. However, it is important to note that this drug was given with a variety of other chemotherapeutic agents (oxaliplatin, irinotecan, leucovorin, cyclophosphamide, methotrexate, doxorubicin, and levamisole), all of which were dosed by actual body weight as well. While our findings may be most relevant to patients receiving a regimen used in one of the larger included studies, the absence of significant heterogeneity in analyses combining findings from patients with a broad range of solid tumor types and chemotherapeutic regimens suggests that the general finding of decreased toxic effects is consistent across a wide range of scenarios. That said, it remains possible that specific chemotherapeutic agents—particularly those under-represented in this meta-analysis—could have excessive toxic effects in obese patients when given in full dose.

It is worth highlighting some important patient groups that are not well represented in the review. We did not include studies that evaluated biologic or immunologic agents or that examined only carboplatin (which is dosed based on kidney function, rather than weight). In addition, though none of the studies in our review explicitly excluded morbidly obese patients (as defined by the WHO as BMI $\geq 40$), none looked specifically at this group, in which concerns about using very high weight-based doses would be the greatest.

Our review had several methodological strengths, including an exhaustive, librarian-assisted search leading to the identification of over 5000 potentially relevant records; broad, well-defined inclusion criteria; and independent and duplicate review for all steps of screening and extracting data. Among the limitations was our need to broaden the definitions of obesity and normal weight in order to accommodate studies that predated the 1995 WHO definitions. Because the older definition (BMI $\geq 27.3$ for females, $\geq 27.8$ for males) used in three studies [14, 42, 46] led to inclusion of both heavier patients in the normal-weight group as well as lighter patients in the obese group, any impact should have skewed the overall findings toward no difference.

Due to the nature of the research question, all studies were observational in design. While most analyses were conducted from a retrospective perspective, the data used were collected prospectively in the highly standardized manner required for chemotherapy trials; patient weight and our outcomes of interest are all routinely collected and objectively measured, thereby minimizing the problems of missing data and reporting bias. Most studies analyzed data from patients enrolled on protocols in which all participants met strict inclusion/exclusion criteria. While these design factors have advantages for increasing internal validity, they can limit generalizability. We recommend that ongoing and future studies routinely provide subset analyses according to BMI categories, and we support additional analyses of BMI-stratified outcome data from previously completed studies of full-dose chemotherapy. However, in order to improve external validity, studies evaluating outcomes of consecutive patients receiving chemotherapy outside of trials, using caution to avoid selection bias, will also be needed.

Another potential area for research is whether doses should be further increased in obese subjects. Evidence suggests toxic effect may be a surrogate marker for efficacy. A recent meta-analysis pooled data from 13 trials that examined neutropenia or leukopenia as a prognostic factor for disease-free or overall survival in cancer patients receiving chemotherapy and demonstrated that patients with higher-grade cytophenias had a 30% risk reduction in mortality compared with patients with...
lower-grade cytopenias [19]. Our finding of lower hematologic toxic effect and possibly poorer survival in obese patients may reflect this phenomenon in which the degree of cytopenia is inversely related to survival. Whether doses should actually be increased in obese patients requires future study and cannot be answered by our analysis.

Our review examined dosing of obese patients using BSA, as this continues to be the standard of care in clinical practice for most chemotherapeutic agents. However, we recognize the shortfalls of BSA-based dosing, which has been shown to have little correlation with pharmacokinetic (PK) measurements for most chemotherapeutic agents [52–58]. Additionally, there is some evidence that doses adjusted for BSA do not produce the same plasma drug concentrations in normal and obese patients [59]. Since as early as 1996, experts have been advising against dosing based on BSA and instead proposing alternate dosing schemes [53]. Therapeutic drug monitoring using pharmacokinetics (PKs) continues to be examined as a more accurate, individualized way to determine dose. However, despite evidence suggesting higher efficacy and/or tolerability of chemotherapeutic regimens with use of PK-adjusted dosing when compared with BSA [60–63], therapeutic drug monitoring (TDM) has not been accepted into widespread practice. Barriers to wider use of TDM include the lack of data on the relationship between the drug concentrations and clinical outcomes, the frequent use of combination chemotherapy regimens complicating assessment of toxic and therapeutic effects for single drugs, the availability of fast and precise assays, and the lack of research funding [64]. None of the studies included in our review incorporated PK measurements. Certainly, use of individualized drug monitoring may ultimately prove most precise for both obese and normal-weight patients. However, given the slow adaptation of individualized dosing approaches, we need to maximize chemotherapy dosing as it is currently administered, and our review consolidates the best-available evidence involving BSA dosing in obese patients.

In conclusion, this review demonstrates that obese patients given doses of chemotherapy based on ABW do not experience more toxic effects than normal-weight patients. By empirically reducing doses in obese patients, oncologists may be doing them a distinct disservice and compromising their chances for experiencing the intended survival benefit of chemotherapy. In the absence of individual contraindications or demonstrated toxic effects, obese patients should receive full-dose chemotherapy based on ABW.

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