Published in final edited form as:

JAMA Oncol. 2015 September ; 1(6): 732–733. doi:10.1001/jamaoncol.2015.1926.

Ovarian cancer survival and chemotherapy dosing, BMI, BSA, are we there yet?

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The study by Bandera et al. evaluated the association of body mass index (BMI) and chemotherapy dosing, and they related relative dose intensity (RDI) to overall and ovarian cancer-specific mortality. This retrospective, cohort analysis was based on the Kaiser Permanente Research on Ovarian Cancer Study of Epithelial Ovarian Cancer (KP-ROCS) chemotherapy sub-cohort (806 patients). Importantly it is a relatively unselected real-world cohort, and one of the largest studied to date. The investigators concluded that lower RDI of paclitaxel and carboplatin was associated with diminished survival in women treated for ovarian cancer which further confirms observations by others [1-4].

For the reader to properly interpret the data presented, it is important to note that terminology matters, and that many terms can serve as confounders for each other. The authors start out by explaining the BSA based dosing of chemotherapy and paclitaxel in particular, with the associated practice of dose capping at higher BSA, which would result in loss of RDI. They reference literature that up to 40% of obese patients receive reduced doses. However, BSA is an absolute size descriptor, while BMI is a descriptor of size relative to height. Someone with a relatively low BSA can have a high BMI and be obese, and vice-versa.

How much of the loss in RDI at higher BMI is potentially attributable to high BSA (and dose-capping) on an individual level remained unanalyzed though at the aggregate level, mean BSA did go up with BMI category. The authors also noted a significant inverse association between BMI and actual dose of paclitaxel and carboplatin per kg of bodyweight. Certainly for paclitaxel this is not a surprise as BSA increased with BMI, and paclitaxel is dosed by BSA (a surface), which increases less than linearly with weight (a volume). Why dose was expressed per kg in the first place is unclear as this is an uncommon

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way to dose chemotherapeutics in the adult setting. An interesting analysis might have been how paclitaxel dose/m^2 trended across BMI categories.

Dose reduction was more common among obese women. Interestingly, this effect was seen across all categories for carboplatin, while for paclitaxel, this effect only truly was visible in patients with BMI>40 kg/m^2, which represented approximately 5% of the population. For carboplatin, the authors rightly point out the potential confounder of physicians utilizing lean body mass in the Cockcroft-Gault (C-G) formula to calculate carboplatin dose, while their calculated reference 100% RDI utilized full mass, thereby overestimating the frequency of dose reduction. This effect plays an important role in the interpretation of the results.

The association of low RDI with ovarian cancer specific survival was only significant for paclitaxel dosed at <70%RDI, which represented 11% of the population. Carboplatin RDI was not associated with survival, potentially due to the previously indicated confounding effect of using lean versus full mass in the C-G formula. Importantly, this means there is no data to support the conclusion that dose reduction of carboplatin is associated with poor survival and that body size is a predictor for carboplatin dose reduction.

The potential survival benefit of obese patients that was observed relative to normal patients, and which was most obvious at average RDI (ARDI)<0.85, may again be attributed to this confounding effect. An ARDI<0.85 in normal patients is more likely a true decrease in RDI resulting in a real survival loss, while the ARDI<0.85 in overweight and obese patients likely consists mostly of artificially low calculated ARDI due to the overestimated frequency of carboplatin dose reduction.

Dose for paclitaxel is calculated based on BSA using one of five or more algorithms all of which include height and weight parameters. This particular study used the Mosteller BSA calculation from 1987 [5]. The original rationale for BSA dosing was to translate the animal dosing to select the human starting dose based on inter-species differences in basal metabolic rates, which track with BSA [6]. BSA based dosing within a species, however, does little to reduce highly variable pharmacokinetics and provides no reliable way to target drug exposure. In only 5 of 33 agents in previous evaluations did BSA-based dosing reduce variability in clearance, and even in those 5 cases, only 35% of variability was explained by BSA [7,8]. Instead of figuring out how to deal with extremes in BMI or BSA, and how to translate this into a BSA-based dose, perhaps investigators should focus their efforts on achieving the right exposure in patients by actually documenting the individual exposure and adjusting the dose based on this most relevant predictor of toxicity and efficacy [9,10].

Only carboplatinum dosing uses a target exposure (AUC-based dosing) and maximum tolerated exposure (MTE); this exposure is rarely documented but rather aimed for through a series of formulas, estimations and assumptions. First, creatinine clearance is estimated from a formula that requires serum creatinine concentration, and anthropomorphic variables including age, weight and sex. Next it is assumed that this estimate is equal to the glomerular filtration rate which loses accuracy as creatinine is in part actively secreted; and lastly, this number is then imputed into the Calvert equation which accounts for the non-

renal elimination of carboplatin, and was derived based on 18 individuals with an R^2 of 0.72 [11]. Bandera et al. noted in their manuscript that the target carboplatin exposure was an AUC of 6 in 75% of patients and an AUC of 5 in 21% of patients. No explanation or speculation regarding this variation was provided, nor if this difference correlated with BMI, though this could impact outcome and equates to RDI<85%.

The authors use the Cockcroft-Gault estimation to calculate a measure of renal function rather than a measured GFR. Cockcroft-Gault estimates creatinine clearance[12]. Brown et al. proposed the use of a CrCl range for drug dosing with the lower boundary defined using ideal body weight and the upper boundary defined by total body weight[13]. As previously pointed out, this range actually spans the difference between full dose and RDI<85%. The requirement of weigh imputation in the C-G formula brings weight based drug dosing full circle. More accurate estimators of CrCl (24 h urine collection) or GFR (^{51}Cr-EDTA, inuline) are associated with collection errors or logistically challenging. It has been shown previously that BMI does not affect outcome and survival if patients receive optimal doses of carboplatinum/taxane chemotherapy based on measured GFR and actual body weight [14].

The conclusion that “body size should not be a major factor influencing dose reduction decisions in women with ovarian cancer” deserves further thought. Does “body size” cover both BSA and BMI? If not a “major” factor, could body size still play a “minor” role in such decisions? Do the authors suggest applying this principle to more chemotherapeutics than merely carboplatinum and paclitaxel, the subject of the current study? The reader is left to struggle with the conundrum of dosing based on BSA, whether to use lean body mass or actual weight in the C-G formula, and whether dose capping still has a place. How to resolve these issues in an evidence-based fashion is challenging. Clearly treatment outcome is closely related to RDI for a number of drugs, but not all drugs are created equal [15]. Decisions on dosing considering size remains both an art and a science until definitive data are generated.

Many studies have looked at dose intensity and outcome, but each used different parameters to determine starting dose adjustment based on BSA or BMI, dose modifications and renal function dependent on BSA. The authors of this manuscript make a valiant effort to resolve some of the issues around the interrelatedness of BMI, BSA, dosing practices, and outcome, and perhaps have made the first and most important step of using a well described, prospectively followed cohort of patients for this analysis. Proper utilization of a well-annotated database may at best obviate the need for very large randomized studies to compare and isolate the impact of BMI, BSA, RDI, the practice of dose-capping, or estimators of renal function in determining dose, on outcome. At worst, such a database will sharpen the questions to be asked in prospective trials. Clinical investigators need to apply the approaches and lessons learned with paclitaxel and carboplatin to other drugs used for the treatment of ovarian cancer: cisplatinum, gemcitabine, liposomal doxorubicin, bevacizumab, olaparib, cediranib, and others. Loss of relative dose intensity at higher BMI will certainly be a problem for some these drugs. Consistent and comprehensive collection of all dosing metrics will allow investigators to perform comparable analyses from a variety of studies.

Acknowledgments

Support: UM1-CA186690 (JHB)

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