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Case Report

Chemotherapy dosing in achondroplastic dwarfism: a case report and review of literature

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SUMMARY

What is known and objective: case description: **A 74-year-old female with achondroplastic dwarfism was diagnosed with ER-, BR- and HER2- breast cancer. No guideline currently exists to direct chemotherapy dosing in this population. She received neoadjuvant chemotherapy based on body surface area utilizing actual height and weight with dose-dense doxorubicin and cyclophosphamide followed by paclitaxel with the use of granulocyte colony-stimulating factor. Satisfactory clinical response and remission were achieved, and treatment proceeded without any significant toxicity or delays.**

What is new and conclusion: **In the absence of guideline recommendations, dosing chemotherapy based on actual height and weight in patients with achondroplastic dwarfism may be safe and appropriate.**

WHAT IS KNOWN AND OBJECTIVE: CASE DESCRIPTION

A 74-year-old female with achondroplastic dwarfism discovered a lump in her left breast upon self-examination. On physical exam, she had a palpable left breast mass of approximately four centimetres that was hard and non-tender with palpitation. A mammogram showed a three-centimetre mass with some speculations in the left breast. This was confirmed by an ultrasound of the left breast. The patient then underwent a left breast core biopsy which resulted in pathology consistent with poorly differentiated invasive ductal carcinoma. Upon testing, this breast cancer was negative for oestrogen receptors (ER−), progesterone receptors (PR−) and human epidermal growth factor receptor 2 (HER2-). Positron emission tomography scan and computerized axial tomography scan were negative for any metastatic disease. Blood work revealed normal complete blood counts and normal renal function with serum creatinine of 0·6 mg/dL and liver function within normal limits. The patient's height was 116·8 cm and her weight was 56·4 kg. Her calculated body surface area (BSA) using Dubois and DuBois formula[1] based on actual height and weight was 1·26 m^2. Based on her height and weight, her body mass index was calculated to be 41·33 kg/m^2, placing her in class III obesity range.

The patient underwent neoadjuvant chemotherapy administered intravenously with dose-dense doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 weeks for a total of four cycles. Granulocyte colony-stimulating factor (GCSF), pegfilgrastim, was given as a 6-mg dose subcutaneously after each cycle. She subsequently received intravenous dose-dense paclitaxel 175 mg/m^2 every 2 weeks for a total of four cycles. GCSF was also administered after each cycle of paclitaxel.

Her chemotherapy was well tolerated without any significant toxicity or delay in her treatment. The only toxicity reported was grade 2 fatigue that occurred after the second cycle of paclitaxel. No haematologic toxicity was observed. Subsequently, the patient had a lumpectomy and sentinel lymph node biopsy which showed only small foci of two millimetre of invasive ductal carcinoma with no tumour seen in the sentinel lymph node. She then received adjuvant radiation therapy. The patient is now currently in remission.

DISCUSSION

Chemotherapy dosing is complex due to several factors. One of those factors is utilizing patient parameters to calculate an appropriate dose in order to achieve therapeutic effects while minimizing toxicity. In an attempt to meet these goals, most chemotherapy dosing regimens are individualized according to patient BSA.[2] This dosing practice is generally used in an effort to achieve normalized drug concentrations across different patient populations as measures of many physiological parameters that are responsible for drug disposition, including renal function and energy expenditure, can be normalized by the use of BSA.[3] American Society of Clinical Oncology (ASCO) guidelines suggest that actual body weight should be used when selecting cytotoxic chemotherapy doses for all patients, regardless of obesity status.[4] However, there is a lack of literature in regard to pharmacokinetic differences within the population of patients with dwarfism. Thus, dosing medications in this subset of patients is challenging, with chemotherapy being particularly difficult due to the narrow therapeutic index associated with many chemotherapy agents.

Since the early twentieth century and the development of the DuBois and DuBois equation, clinicians have utilized BSA to guide dosing of medications.[2] In the 1960s, this formula became

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routinely considered when dosing anticancer chemotherapy agents.[5] When dosing chemotherapy, appropriate dosing is particularly critical as lower dose intensity may compromise disease control and survival in patients with curable malignancies[5] and higher dose intensity may lead to severe toxicities.[5] As the equation commonly used to determine BSA were developed using a relatively homogenous population of eight patients, the applicability to patients whose measurements fall outside of the normal parameters, such as those achondroplastic dwarfism, is unknown.

Achondroplastic dwarfism causes differences in body composition compared to the average adult. Expressing obesity in regard to weight for sex, height and frame is not applicable in patients with skeletal dysplastic diseases. Unfortunately, indices from weight and height have not been examined for those with dwarfism which tends to be heterogenous.[6] In a study assessing the metabolic rate and body composition of this population, abdominal circumference ratios were not predictive of body fat and body mass indices were not indicative of body fat.[6] Skinfold thicknesses and other anthropometric measurements were of very limited value in predicting the body fat of patients with dwarfism.[6] Kaur *et al.*[7] reported a case of a patient with achondroplastic dwarfism who underwent unsuccessful rapid sequence induction resulting in the patient not being able to be intubated on the first attempt. Actual body weight was utilized in dosing this patient's anaesthesia, and doses had to be increased beyond weight-based amounts. The authors felt that unsuccessful intubation might have been due to the differences in body structures of these patients as well as differences in lean body weight and overall body weight.

To further complicate dosing patients of atypical body composition, the proportion of different tissue types varies between individuals of the same body size. Gusella *et al.*[8] found that after fluorouracil bolus doses, fat-free mass and total body water were better predictors of fluorouracil clearance and volume of distribution, respectively, than both body weight and BSA. The use of lean body mass was a better predictor of epirubicin clearance[9] but was less satisfactory in the case of irinotecan.[10] This variability in the limited available data offer no guidance for dosing patients with atypical body composition such as patients with achondroplastic dwarfism.

Regarding the specific chemotherapy medications this patient received, several studies have demonstrated variable guidance regarding dosing patients of atypical body size. In a study comparing the pharmacokinetics of doxorubicin in normal-weight, mildly obese and obese patients, doxorubicin was shown to have a longer elimination half-life in obese group compared to the normal-weight group (20·4 h vs. 13·0 h, respectively) while the apparent volume of distribution was similar.[11] The authors concluded that the prolonged half-life in obese patients was related to reduction in clearance, not volume of distribution. Similar results were found in a study of pharmacokinetics of cyclophosphamide in sixteen female patients with advanced breast cancer.[12] The authors reported a positive correlation between plasma elimination half-life and body weight, negative correlation between cyclophosphamide clearance and BSA and no correlation between volume of distribution and body weight. However, adjusting dosages based on obesity status should be considered cautiously due to the narrow therapeutic range of chemotherapy. In a retrospective cohort study of over nine thousand women who were treated with doxorubicin and cyclophosphamide for breast cancer, 37% of severely obese women received first-cycle dose reduction, defined as a dose equalling less than 90% of standard published doses.[13] Sixteen per cent of all patients in this study received an additional cycle and thirteen per cent received a sixth cycle beyond the standard four cycles, increasing the overall total dose patients were exposed to without providing the benefits of dose intensity (e.g. 'dose-dense' chemotherapy).

Various physiological and pathological factors are known to affect drug exposure and drug clearance. Hepatic function, renal function, BSA, obesity, body composition, nutritional status, enzyme expression, drug resistance, drug-binding plasma proteins, gender, age, disease and concomitant drugs can all affect drug-related activity and antitumour activity.[14] Differences in body mass and size do not necessarily affect the size or functionality of organs involved in drug elimination.[15] Therefore, it may not be logical to adjust the dose based solely on the body composition differences of patients with achondroplastic dwarfism.

As previously mentioned, the ASCO guidelines suggest that actual body weight should be used when selecting cytotoxic chemotherapy doses for all patients regardless of obesity status.[4] Using the standard method for calculating body mass index classifies this patient in class III or high-risk obesity range. Using actual body weight appears to be more fitting based on ASCO recommendations to those with achondroplastic dwarfism when calculating BSA for dosing as their weight-to-height ratios may not accurately represent their body composition with regard to obesity status.

Extended toxicity of chemotherapy regimens are not well studied in the population of those with achondroplastic dwarfism. Due to the lack of studies or guidelines providing guidance on how to dose chemotherapy in this population and based on the data previously mentioned questioning the utility of anthropometric measures, actual body weight and height with no adjustment were incorporated for this patient when calculating BSA to choose a dose. The patient tolerated treatment well without any significant toxicity, and she had a very good response to chemotherapy as evidenced by only small foci of two millimetre of invasive ductal carcinoma that was managed with adjuvant radiation.

WHAT IS NEW AND CONCLUSION

To our knowledge, this is the first case reported about chemotherapy use in a patient with achondroplastic dwarfism. Based on this experience gained through dosing this patient, chemotherapy dosing using BSA based on actual height and weight was appropriate and safe. However, further studies are required to have a better understanding of the pharmacokinetics and optimal dosing of chemotherapy in this special population.

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