

Dose Rounding of Cytotoxic Drugs and Monoclonal Antibodies

A Position Statement of the Hematology/Oncology Pharmacy Association

Background/Executive Summary:

The cost of cancer care in the United States is expected to exceed 170 billion dollars in 2020 and represents one of the fastest growing costs in health care. ¹ Rounding of drug doses to the nearest vial size when the difference is less than an established percentage is an important initiative that can be implemented to minimize drug waste, ensure accuracy during drug preparation, and reduce healthcare expenditures. Dose rounding is especially relevant for drugs that are supplied in single-use vials in a preservative-free formulation. The Centers for Medicare and Medicaid Services allow billing for wasted doses from single-use vials, but this policy benefits reimbursement, not cost or waste reduction. Various institutions have implemented dose rounding policies, which generally allow dose rounding within 5 to 10 percent of the ordered dose for biologic and cytotoxic anticancer treatments. ²⁻⁴ Some institution-specific policies permit more liberal rounding with monoclonal antibodies versus cytotoxic chemotherapy and/or in the setting of palliative versus curative intent. Although the impact of dose rounding on disease progression or overall survival is expected to be non-influential, few studies have evaluated this question. Single institution cost analyses estimate savings ranging from tens of thousands to millions of dollars depending on the drug and the number of doses dispensed per patient per year. ²⁻⁸

Some centers may avoid dose rounding for pediatric patients or patients under a designated weight due to the futility of dose rounding for amounts consistently much smaller than the vial content amounts. ⁹ Although this position statement does not include data from the pediatric population it would not be unreasonable for clinicians to utilize the recommendations herein for larger pediatric patients or adult patients being treated on pediatric protocols based on clinical judgment.

Monoclonal Antibodies Dose Rounding

Recommendation 1: Based on the limited published data, HOPA recommends that monoclonal antibodies and other biologic agents currently available be dose rounded to the nearest vial size within 10 percent of the prescribed dose.

Recommendation 2: For monoclonal antibodies with a cytotoxic constituent HOPA favors using the dose rounding recommendation applied to cytotoxic agents.

Monoclonal antibodies and other biologic therapies (e.g. interleukin and interferon) provide a targeted therapeutic effect towards tumor cells. ¹⁰ The pharmacologic mechanism of action varies and may include disruption of a biologic messaging process (e.g. cetuximab), cellular cytotoxicity (e.g., rituximab), or delivery of a toxic conjugate (e.g., brentuximab vedotin). Due

to the complex processes to manufacture, monoclonal antibodies are expensive to produce.³ Monoclonal antibodies are administered intravenously and most are packaged as single-use, preservative-free vials, resulting in one-time use and short beyond use dating.⁵

Dose rounding of multiple monoclonal antibodies has been reported in the literature, including rituximab, bevacizumab, trastuzumab, cetuximab, ipilimumab, and gemtuzumab.^{2,3} Current literature focuses on the impact of dose rounding on cost savings and medication waste reduction, however, studies have not addressed the effects of dose rounding on efficacy.³ Dose rounding options reported in the literature include rounding to the nearest vial size if the rounded dose falls within 10 percent of the prescribed dose,² rounding down to the nearest vial size if the dose falls within 5 or 10 percent of the prescribed dose,³ and rounding to the nearest vial size increment (i.e. 50 mg vial for ipilimumab).⁵ In one example, projected annual savings for rounding bevacizumab, trastuzumab, and cetuximab down to the nearest vial size within 5 and 10 percent of the prescribed dose were \$181,944 and \$337,755, respectively.³ Winger and colleagues showed a cost savings of \$124,434 over a 3-month time period for seven biologic anticancer agents when rounding biologic agents within 10 percent to nearest vial size.⁴

Monoclonal antibodies have been tested using a wide range of doses, with some drugs not reaching a maximum tolerated dose. Nivolumab has been evaluated in doses ranging from 0.1 to 10 mg/kg, and a maximum tolerated dose (MTD) was not reached within this dosing range.¹¹ Weber and colleagues reported giving multiple doses up to 10 mg/kg and single dosing up to 20 mg/kg of ipilimumab without reaching a maximum-tolerated dose.¹² Ipilimumab FDA approved dosing ranges from 3mg/kg to 10mg/kg based on indication.¹³ These examples illustrate monoclonal antibodies have a wide therapeutic dosing range. Moreover, pharmacokinetic studies have demonstrated significant inter-patient variability in drug exposure. As Table 1 demonstrates, the coefficients of variation (CV) for the area under the curve (AUC) measurements for biologic drugs can vary significantly. The wide therapeutic dosing range and CV for AUCs for the monoclonal antibodies support liberal rounding without raising safety signals.

Table 1. CV for the AUC measurements for biologic anticancer drugs	
Drug	Percent
ado-trastuzumab	11-34
bevacizumab	15-53
brentuximab vedotin	25-30
cetuximab	22-65
ipilimumab	25-36
rituximab	45
trastuzumab	25-35
ziv-aflibercept	15-37

For antibody-drug conjugates (ADCs), which are defined as a monoclonal antibodies linked to a cytotoxic constituent (such as ado-trastuzumab emtansine), rounding recommendations can follow either those of monoclonal antibodies or cytotoxics. One center reported dose rounding within 10 percent for ADCs, thus classifying them as biologics for dose rounding purposes.^{4,9} The reasoning for categorizing ADCs as biologics is that the targeted delivery of the cytotoxic constituent is conferred by its conjugation to a monoclonal antibody. In contrast, support for categorizing ADCs as cytotoxics is made based on the toxic potential of the cytotoxic constituent. Some institutions round ADCs based on the monoclonal antibody carrier while others round ADCs based on the cytotoxic component. Arguments can be made for both but HOPA prefers the conservative approach of rounding ADCs per the cytotoxic rounding recommendations due to the narrower therapeutic range of these drugs

Cytotoxic Chemotherapy Dose Rounding

Recommendation 3: Based on the available literature, HOPA recommends that traditional cytotoxic agents should be considered independently for dose rounding within 10 percent of the prescribed dose.

The rationale for rounding to an amount within 5 to 10 percent of an ordered dose is based on the premise that this will not negatively impact safety or effectiveness of therapy. Although experience with dose rounding of traditional cytotoxic chemotherapy is less well published, the potential impact and feasibility of a 5 percent rounding allowance for cytotoxic drugs has been evaluated and published in multiple reports.^{6,9} Cytotoxic chemotherapeutic agents are traditionally considered to have a narrow therapeutic index. Doses approved for treating malignancies are usually based on MTDs defined in clinical trials. MTDs are determined in phase I studies using dose escalation methods, often increasing doses by 25 percent or more. When a MTD is reached, the dose level below the defined toxic level is recommended for further investigation in larger phase II studies.¹⁴ One example is pemetrexed 600 mg/m², which was chosen as a safe dose in phase I trials, but due to bone marrow suppression and gastrointestinal toxicity, the dose was empirically reduced to 500 mg/m². This reduction occurred prior to the discovery that vitamin supplementation reduces these toxicities. Therefore, with appropriate ancillary medication therapy, it is reasonable that a dose in the range of 450 to 550 mg/m² can be given safely and effectively to avoid drug waste.¹⁵ A dose escalation strategy for liposomal doxorubicin involved 7 dose levels from 20 mg/m² up to 40 mg/m² increasing the dose by 25 to 50 percent between dose levels.¹⁶ Furthermore, standard dose adjustments to improve patient tolerance and response are generally in the range of 20 to 30 percent, which exceeds the amounts for reported dose rounding amounts by several fold. Rounding cytotoxic agents by 10 percent seems safe in the context of the amount of dose adjustments made for patient tolerance and tumor response (≥ 20 percent). Moreover, dose rounding in amounts of 10 percent for both cytotoxic and biologic products streamlines the process for staff.

An additional consideration is that despite surface area- and weight-based dosing for most anticancer treatments, the effect of dose adjustments within 10 percent on the AUC will generally be eclipsed by the degree of inter-patient pharmacokinetic variability that ultimately determines systemic drug exposure.⁹ One study reported that systemic concentrations of only 5 of 33 investigational anticancer drugs (docosahexaenoic acid–paclitaxel, fluorouracil/eniluracil, paclitaxel, temozolomide, and troxacitabine) administered to 1650 patients were normalized with the surface area-based dose calculation. The CV for drug clearance ranged from 13 to 151 percent and 22 to 170 percent for orally and intravenously administered drugs, respectively.¹⁷

Potential Differences in Dose Rounding Limits Depending on the Intent of Treatment

Recommendation 4: Based on the inference that dose rounding will not influence clinical safety or effectiveness HOPA supports use of the same threshold for dose rounding of anticancer drugs utilized for palliative and curative therapy.

Some providers support dose rounding within 10 percent for palliative therapy and within 5 percent for curative therapy. This is based on the notion that the balance of patient safety and effectiveness differs between palliative and curative therapy.^{2, 3, 11} Standard dose adjustments to improve patient tolerance and response are generally in the range of 20 to 30 percent, which exceeds the amounts reported for dose rounding amounts by several fold.^{8, 14, 15}

Dose Rounding Recommendations for Oral Chemotherapy

Recommendation 5: When oral chemotherapy is supplied in more than one strength of capsule or tablet, it is advantageous to use one strength and to round the final dose to avoid confusion for the patient and to eliminate the possibility of multiple copayments.

Dose rounding of oral oncolytics is not well published and is limited to the tablet or capsule size of the drug. The majority of oral oncolytics have flat-based dosing, while some are dosed on BSA and weight. Oral oncolytics should not be crushed, or cut and should be swallowed whole. Prescribing multiple strengths of an oral medication increases the opportunity for medication errors.¹⁸ According to the American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, doses may be rounded to the nearest capsule or tablet size.¹⁹

Implementation of an Institutional Dose-Rounding Policy

Recommendation 6: Institutions should develop policies through interdisciplinary efforts, which can be endorsed by a policy-managing body such as a Pharmacy and Therapeutics (P&T) committee or an oncology subcommittee. The policy should describe which cytotoxic and monoclonal antibody classes are subject to dose rounding, rounding limits for each class, the process for rounding ordered doses, documentation of such changes, and any applicable exceptions such as drugs supplied in multi-dose vials or circumstances where prescribers should be consulted prior to rounding by the pharmacist.

Below contains example of wording that maybe added to a current chemotherapy policy:

Chemotherapy dose rounding: Ordered chemotherapy doses may be rounded up or down by *** percent, by the pharmacist during the verification process without prior authorization of the ordering physician. This may be done to avoid drug waste and is approved by ____ policy that was approved by the ____ committee on ____>

For orders where dose rounding has been applied, reference to the ordered dose and the rounded dose should be readily available (i.e. documentation on the MAR and/or prescription label). Example wording of documentation: Dose changed from *** mg to *** mg per dose rounding policy. Change within ***%. (dosed at ***mg/****) pharmacist name and date of change. These references serve to document the application of rounding practices and provide opportunities for other care providers to independently validate the rounding and assess its appropriateness for the patient. When possible, dose rounding should be automated by the electronic health record in accordance to institutional policy. Automated rounding removes the need for manual entry of the rounded dose which is an opportunity for human error.

Exceptions

Each institution should establish exceptions to its dose rounding policy. Such exceptions include drugs that patients receive in the clinical trial setting, since dose rounding could be considered a breach of protocol.⁹ Patients with multiple chronic comorbidities, relevant enzyme deficiencies, or genetic polymorphisms may not be good candidates for dose rounding upwards since small adjustments in the dose could result in significant pharmacokinetic changes and subsequently significant adverse events. Dose rounding for pharmacokinetically determined doses of anticancer treatments, such as parenteral busulfan, may not be appropriate, especially when rigorous data is needed for institutional data tracking or research analysis.⁹

Summary

HOPA recommends that each institution develop its own dose rounding policy that addresses both monoclonal antibodies and cytotoxic drugs. Institutions may consider rounding both monoclonal antibodies and cytotoxic drugs by the same percentage for consistency.

Institutional guidelines for dose rounding of anticancer agents should be based on a collaborative interdisciplinary consensus. Each institution should also establish its own criteria for automatic dose rounding, the allowable percentage, and the process to operationalize and document any modifications to the original prescribed dose. Exceptions to the dose rounding policy should be determined a priori. Dose rounding represents a relatively simple cost-savings measure that institutions can implement to reduce waste and health care costs.

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