The National Academies of Sciences, Engineering, and Medicine Committee on Implications of Discarded Weight-Based Drugs

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A Bit of History

- BSA dosing of chemotherapy drugs first proposed in 1956 based on correlations with metabolic rates and blood volume
- Goal to normalize dose and reduce inter-individual variation in drug effects
- Standard practice for drug dosing despite limited impact on reducing variability
- Chemotherapy doses empirically determined by establishing MTD in patients with advanced cancer
- For most cancer drugs, little relationship between body weight and drug clearance, toxicity or efficacy
- Therapeutic drug monitoring not proven useful in oncology, with exception of MTX
- ASCO Guidelines recommend dosing of obese patients based on actual (not ideal) body weight; no preference for BSA formula
- **Little rationale for weight-based dosing other than historical precedent**
- Alternatives: Dose-banding; Fixed dosing

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Targeted Small Molecules and Antibodies

- Dosing often determined by plasma concentration required to achieve target inhibition or receptor occupancy, “optimum biological dose”
- Typically display saturable kinetics so more is not better
- Large proteins cleared through receptor binding or intracellular catabolism with nonlinear clearance
- Fixed dosing and weight-based dosing perform similarly across therapeutic monoclonal antibodies
- Prescribing information for both nivolumab and pembrolizumab changed from weight-based to fixed dosing for most indications
- All orally active targeted therapies have used fixed-dosing schemes

Pembrolizumab

- In clinical trials, administered at 2 mg/kg IV Q 3w, 10 mg/kg IV Q 2w, 10 mg/kg IV Q 3w, or 200 mg intravenously
- First approved 2014 (melanoma; 2mg/kg IV Q 3w; supplied as 50 mg, lyophilized powder in single-dose vial)
- Current indications: Melanoma, NSCLC, HNSCC, Hodgkin Lymphoma, Mediastinal B Cell Lymphoma, Urothelial Cancer, MSI-H Cancers, Gastric Cancer, Cervical Cancer, Hepatocellular Cancer, Merkel Cell Cancer, Renal Cell Cancer
- Adult dosing for all indications: 200 mg IV Q 3w, infused over 30 min; Pediatric dose 2 mg/kg
- Supplied: 50 mg lyophilized powder in single-dose vial and 100 mg/4 mL solution in a single-dose vial

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Nivolumab

- Initial approval 2014 for melanoma, 3 mg/kg Q2w
- Subsequent indications: Adjuvant melanoma, NSCLC, renal cell, Hodgkin lymphoma, HNSCC, urothelial cancer, MSI-H CRC, Hepatocellular cancer
- Most single agent trials studied of doses 3 mg/kg Q2w
- Current single agent dosing: 240 mg Q2w or 480 mg Q4w
- Supplied as: 40 mg/4 mL, 100 mg/10 mL, and 240 mg/24 mL solution in a single dose vial

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Bevacizumab

- Initial approval 2004, CRC
- Subsequent indications: NSCLC, GBM, RCC, Ovarian/fallopian/primary peritoneal cancer, Cervical cancer
- Dose varies with indication: 5 mg/kg Q2w; 10 mg/kg Q2w; 7.5 mg/kg Q3w; 15 mg/kg Q3w
- Supplied: 100 mg/4 mL or 400 mg/16 mL in a single-dose vial
- Dose for 70 kg patient (10 mg/kg) is 700 mg, 1-400 mg vial + 3-100 mg vials; Dose at 15 mg/kg is 1050 mg, 2-400 mg vials + 3-100 mg vials. 50 mg wasted without rounding
- Billing unit is 10 mg (J9035)

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Rituximab

- Approved for use 1997, non Hodgkin Lymphoma; subsequently CLL
- Dose: 375 mg/m^2 for NHL; for CLL: 375 mg/m^2 cycle 1 then 500 mg/m^2 cycles 2-6 with chemo
- Supplied: 100 mg/10 mL and 500 mg/50 mL single use vials
- For 1.8 m^2 patient, calculated dose is 675 mg. Requires 1-500 mg vial plus 2-100 mg vials with 25 mg wasted. Billing unit is10 mg (J9312)

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The Cost of Drug Waste

- In 2017, Medicare required the use of the billing modifier "JW" to specify the number of units discarded as waste
- ASCO analyzed data from 17 Oncology Care Model practices for a two-year period (January 2017 to December 2018)
- $538M in IV drug spend
- $21M drug waste, identified by the "JW" modifier
- 3.9%

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Top Drug Spend

OCM PERIOD	ADMINISTERED	WASTED (JW)	% OF TOTAL
Bortezomib	$9,954,534	$4,534,100	31.3%
Trastuzumab	27,132,274	2,503,474	8.4%
Nab-paclitaxel	7,301,282	1,568,738	17.7%
Pembrolizumab	51,913,225	1,328,779	2.5%
Carfilzomib	7,094,314	1,093,585	13.4%
Cabazitaxel	2,782,121	1,077,824	27.9%
Bevacizumab	32,589,794	1,042,667	3.1%
Ipilimumab	8,849,987	792,898	8.2%
Decitabine	2,218,752	775,496	25.9%
Azacitidine	1,846,247	681,598	27.0%

73% of oncology drug waste spend is from ten drugs.

For four drugs, the wasted amount totaled over 25% of their total spend.

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Dose Banding Models from NHS England

Balanced

NHS England

National Dose Banding Table – Rituximab

Vial Sizes of Drug	100mg/10mL 500mg/50mL	Drug	Rituximab

Band Range (mg)			Band Dose (mg)	Variance (%)	
From	To (A) <	To (B) ≤		Below	Above
748.33	848.53	848.52	800	6.9	-5.7
848.53	948.68	948.67	900	6.1	-5.1
948.68	1048.81	1048.80	1000	5.4	-4.7
1048.81	1148.91	1148.90	1100	4.9	-4.3
1148.91	1249.00	1248.99	1200	4.4	-3.9
1249.00	1349.07	1349.06	1300	4.1	-3.6

https://www.england.nhs.uk/wp-content/uploads/2017/09/national-tables-rituximab-10mgml-v4.pdf

Value-Based

NHS England

National Dose Banding Table – Bevacizumab (Avastin®)

Vial Sizes of Drug	100mg/4mL 400mg/16mL	Drug	Bevacizumab (Avastin®)

See table usage notes below regarding 'single container' and 'multiple syringe' tables.

Band Range (mg)			Band Dose (mg)	Variance (percent)	
From ≥	To (A) <	To (B) ≤		Below	Above
100.00	113.00	112.99	100	0	-12
113.00	141.00	140.99	125	11	-11
141.00	169.00	168.99	150	6	-11
169.00	196.00	195.99	175	4	-11
196.00	221.00	220.99	200	2	-10
221.00	250.00	249.99	225	2	-10
250.00	280.00	279.99	250	0	-11
280.00	332.00	331.99	300	7	-10
332.00	390.00	389.99	350	5	-10
390.00	446.00	445.99	400	3	-10
446.00	500.00	499.99	450	1	-10
500.00	550.00	549.99	500	0	-9
550.00	600.00	599.99	550	0	-8
600.00	661.00	660.99	600	0	-9
661.00	771.00	770.99	700	6	-9
771.00	881.00	880.99	800	4	-9
881.00	1000.00	999.99	900	2	-10
1000.00	1100.00	1099.99	1000	0	-9

https://www.england.nhs.uk/wp-content/uploads/2018/04/national-tables-bevacizumab-25mgml-v2.pdf

Benefits of Dose Banding

- Can simplify dose preparation through use of fewer vials
- Can provide for repackaging through a USP General Chapter 797 compliant compounding pharmacy
  - e.g. repackaging a 100mg vial of rituximab into two 50mg vials
- Reduce overall drug spend
  - e.g. NHS England rounds down most bevacizumab doses, eliminating waste and reducing drug spend

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Concerns about Repackaging

- Use of single-use vials for multiple patients is not allowed[1,2]
- Repackaging allowed under ISO Class 5 air quality conditions, following USP General Chapter 797[3]
  - However, the CDC recommends that it be done only when there is a critical need, e.g. shortage
- Risks of repackaging precludes this as a common practice at many cancer centers without a compounding pharmacy

[1] https://www.cdc.gov/injectionsafety/cdcposition-singleusevial.html
[2] https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-12-35.pdf
[3] https://www.usp.org/compounding/general-chapter-797

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Agency Guidance Inconsistent

- FDA: "Significantly more drug than is required for a single dose may result in the misuse of the leftover drug product. Similarly, the need to combine several single-dose vials for a single patient dose may lead to medication errors and microbial contamination"
- CMS: "It is permissible for healthcare personnel to administer repackaged doses derived from SDVs to multiple patients, provided that each repackaged dose is used for a single patient in accordance with applicable storage and handling requirements"
- CDC: "Vials labeled by the manufacturer as 'single dose' or 'single use' should only be used for a single patient. These medications typically lack antimicrobial preservatives and can become contaminated and serve as a source of infection when they are used inappropriately"

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ASCO Policy Initiatives

- Harmonize FDA, CMS, CDC guidance
- JW modifier useful for documentation; should not be used for payment adjustment
- Portman amendment (to Senate drug pricing bill): would require a manufacturer… to refund to CMS the amount of payment made to providers for unused amounts of single-use vials that exceed a minimum threshold. Requires HHS to conduct periodic audits on payment claims submitted by providers. Concern about reporting burden for physicians. Patients not reimbursed for co-pays.

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