Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

Dear Colleagues,

Hope you all are doing well and staying safe from the COVID-19 pandemic.

Harmonization of Busulfan Plasma Exposure Unit (BPEU): A Community-Initiated Consensus Statement (Biol Blood Marrow Transplant. 2019;25(9):1890-1897) published last year recommends that busulfan AUC be reported in **mg x h/L** unit (harmonized unit). This is also known as busulfan plasma exposure units (BPEU). The consensus statement proposes that the harmonized units should be the only unit used to express busulfan plasma exposure (or the AUC) by January 1st 2021. A number of our client institutions have approached the Seattle Cancer Care Alliance (SCCA) Pharmacokinetics (PK) Laboratory regarding the possibility of using BPEU on the busulfan PK report. We are writing this letter to apprise all of you with our plan to implement reporting busulfan exposure using the harmonized units in the near future.

To comply with the proposed timeline, facilitate transition and help our client institutions familiarize with the harmonized units, the SCCA PK lab has put together the following plan which will begin by September 1, 2020.

- Report busulfan exposure in both your institution's preferred units and the harmonized BPEU of mg x h/L.
- Provide a conversion chart available as a quick glance to rapidly visualize busulfan exposure among the three most commonly used units AUC in uMolar x min, AUC in mg x h/L, and Css in ng/mL.
- We are also available to walk you through the unit conversions via email and verbally as needed.

Several additional tools are available to assist you as well:

- ASTCT conversion units app (included in the "ASTCT Practice Guidelines" app) for computer desktop and smartphone app. http://tgapp.asbmt.org
- Github repository managed by ASTCT (https://github.com/busulfanpk/busulfan-pharmacokinetics), provides an updated Technical Appendix and a Microsoft Excel spreadsheet converting between the most common BPEUs.

Please email the PK lab if your institution does not wish to participate in the pilot reporting process with two different busulfan exposure units. In such a case, busulfan PK reports for your institution will remain unchanged. Also, please do not hesitate to contact us if you have any questions.

Best regards,

Seattle Cancer Care Alliance (SCCA) Pharmacokinetics Laboratory

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Busulfan Conversion Chart (Total AUC units assume four (4) total days busulfan)

Total AUC (Four-Day Regimen)		Q24 AUC (per dose)		Q6 AUC (per dose)		Css
mg x h/L	uMolar x min	mg x h/L	uMolar x min	mg x h/L	uMolar x min	ng/mL
30.0	7308	7.50	1827	1.88	457	313
33.6	8185	8.40	2046	2.10	512	350
38.4	9354	9.60	2339	2.40	585	400
40.0	9744	10.00	2436	2.50	609	417
43.2	10,524	10.80	2631	2.70	658	450
45.0	10,962	11.25	2741	2.81	685	469
48.0	11,693	12.00	2923	3.00	731	500
50.0	12,180	12.50	3045	3.13	761	521
52.8	12,862	13.20	3216	3.30	804	550
55.0	13,398	13.75	3350	3.44	837	573
57.6	14,032	14.40	3508	3.60	877	600
59.1	14,397	14.78	3599	3.69	900	616
60.0	14,616	15.00	3654	3.75	914	625
62.4	15,201	15.60	3800	3.90	950	650
65.0	15,834	16.25	3959	4.06	990	677
65.7	16,005	16.43	4001	4.11	1000	684
67.2	16,370	16.80	4093	4.20	1023	700
70.0	17,052	17.50	4263	4.38	1066	729
72.0	17,540	18.00	4385	4.50	1096	750
72.3	17,613	18.08	4403	4.52	1101	753
73.9	18,002	18.48	4501	4.62	1125	770
75.0	18,270	18.75	4568	4.69	1142	781
76.8	18,709	19.20	4677	4.80	1169	800
78.0	19,001	19.50	4750	4.88	1188	813
78.8	19,196	19.70	4799	4.93	1200	821
80.0	19,488	20.00	4872	5.00	1218	833
81.6	19,878	20.40	4970	5.10	1242	850
82.1	20,000	20.53	5000	5.13	1250	855
85.0	20,706	21.25	5177	5.31	1294	885
86.4	21,048	21.60	5262	5.40	1315	900
87.0	21,194	21.75	5298	5.44	1325	906
90.0	21,924	22.50	5481	5.63	1370	938
90.3	21,998	22.58	5499	5.64	1375	941
91.2	22,217	22.80	5554	5.70	1389	950
95.0	23,143	23.75	5786	5.94	1446	990
96.0	23,386	24.00	5847	6.00	1462	1000
98.5	23,995	24.63	5999	6.16	1500	1026
100.0	24,361	25.00	6090	6.25	1523	1042
101.0	24,604	25.25	6151	6.31	1538	1052
105.0	25,579	26.25	6395	6.56	1599	1094
110.0	26,797	27.50	6699	6.88	1675	1146

Busulfan molar mass (molecular weight) = 246.3 gram/mole, https://pubchem.ncbi.nlm.nih.gov/compound/2478

Seattle Cancer Care Alliance, Pharmacokinetics Laboratory. Version 1.2, updated 8.18.2020.

Conversion Equations

Abbreviations Used: AUC, Area-under-the-curve; Css, Concentration at steady-state

Important Notes:

- AUC exposure targets using the harmonized units of $\frac{mg \times h}{L}$ are typically expressed as cumulative AUC.
- Conceptually, Css is measured for an individual dose or an average over time, thus a cumulative exposure cannot be directly measured in Css.

Key Equations:

Eq. 1: Convert from Css in $\frac{ng}{mL}$ to AUC in harmonized units of $\frac{mg \times h}{L}$

$$\frac{\text{Css in } \frac{ng}{mL} \times \text{dosing frequency in hours}}{1000} = \text{AUC in } \frac{mg \times h}{L} \text{ per dose}$$

Estimated Cumulative AUC = Per dose AUC × total # of doses

Eq. 2: Convert from AUC in µMolar × min to AUC in harmonized units of $\frac{mg \times h}{L}$

$$\frac{\text{AUC in } \frac{\mu moles \times min}{L} \times 246.3}{60{,}000} = \text{AUC in } \frac{mg \times h}{L} \text{ per dose}$$

Note: $\frac{\mu moles \times min}{L}$ = µMolar × min

Busulfan MW = 246.3 g/mole

Examples,

Ex. 1: Convert Css of 900 ng/mL to harmonized units (busulfan administered every 24-hours)

Using above Eq. 1,

$$\frac{900 \frac{ng}{mL} \times 24 \text{ hours}}{1000} = 21.6 \frac{mg \times h}{L} \text{ per dose}$$

For a 4-dose regimen, cumulative AUC = $4 \times 21.6 \frac{mg \times h}{L} = 86.4 \frac{mg \times h}{L}$ cumulative AUC

Ex. 2: Convert Css of 900 ng/mL to harmonized units (busulfan administered every 6-hours)

Using above Eq. 1,

$$\frac{900 \frac{ng}{mL} \times 6 \text{ hours}}{1000} = 5.4 \frac{mg \times h}{L} \text{ per dose}$$

For a 16-dose regimen, cumulative AUC = $16 \times 5.4 \frac{mg \times h}{L} = 86.4 \frac{mg \times h}{L}$ cumulative AUC

Ex. 3: Convert AUC of 5262 µMolar × min (either per dose or average AUC) to harmonized units, once daily administration

Using above Eq. 2,

$$\frac{5262 \frac{\mu moles \times min}{L} \times 246.3}{60{,}000} = 21.6 \frac{mg \times h}{L} \text{ per dose or average AUC}$$

For a 4-dose regimen, cumulative AUC = $4 \times 21.6 \frac{mg \times h}{L} = 86.4 \frac{mg \times h}{L}$ cumulative AUC