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S1 Text

Discussion on delays in treatment-induced apoptosis due to pharmacokinetics and pharmacodynamics

A. Time delays vs. final tumor volumetric measurement (CT acquisition)

Let's assume a hypothetical tumor with an initial population of 100 cells. The tumor is treated with a single dose of chemotherapy corresponding to a cell kill rate (CKR) equal to 0.4. The chemo kills 40 cancer cells, resulting in a final population of 60 tumor cells. Let's also assume that in the simulated tumor, lethally hit cells disappear at the instance of drug administration. In reality, lethally hit cells will occupy space in the tumor for some time before their permanent removal. This time will depend on the pharmacokinetics and pharmacodynamics of the drug. If CT acquisition takes place while the effect of treatment is still ongoing, e.g. when only 20 out of 40 cells have disappeared and, hence, the tumor consists of 80 cells, then the estimated CKR will be less, because it will be derived assuming a higher final volume. On the other hand, if the tumor is measured after the completion of the treatment effect, then the estimated CKR will be accurate, regardless of the exact time point of measurement. It should be noted that, in the above example, the proliferation during and after treatment is ignored for simplicity reasons, without loss of generality; however, it is explicitly modelled in our approach. Moreover, in our approach, lethally hit cells are not removed from the tumor instantaneously but follow a rudimentary cell cycle that leads them to apoptotic death.

Additional time delays in the permanent removal of lethally hit cells are expected due to the method of administration (infusion in our cases), and the specific pharmacokinetics and pharmacodynamics of the drug. Table A and B lists characteristic pharmacokinetic and pharmacodynamic properties of the drugs considered in the present work. For example, in the case of cisplatin, maximum plasma concentration is reached at the end of infusion (pharmacokinetics) [Delord *et al.*, 2009], thus 1 hour after drug administration, whereas the drug may cause a cell arrest of a couple of days (pharmacodynamics), before the triggering of the apoptotic mechanism, in an attempt of the cell to repair its damages. The consideration of these delays are determinant when the final CT acquisition takes place while the effect of therapy is still ongoing. However, in all cases, the final CT acquisition takes place in the very late terminal phase of elimination of the last drug dose and the interval between final CT acquisition and last drug administration is long enough relative to both the terminal half-life of the drug (Table C) and the possible delays due to the drug pharmacodynamics (Table B). It should be noted that this late terminal phase has no therapeutic significance but rather represents drug persistence in body.

B. Time delays vs. dosage intervals

In all dosage regimens, the interval between consecutive administrations of the same drug is large relative to terminal half-life (Table C). The doses are administered in the very late terminal phase of elimination of the previous one, when the residual plasma concentration is either below the detection limit (e.g. cisplatin, gemcitabine) or corresponds to a very small fraction (<1%) of the maximum concentration (e.g. vinorelbine on day 8 of each cycle and docetaxel). Therefore, no drug accumulation is anticipated [Delord *et al.*, 2009; Fan *et al.*, 2010; Brunsvig *et al.*, 2007; de Lange *et al.*, 2005].

Table A. Pharmacokinetic properties of cisplatin, docetaxel, gemcitabine and vinorelbine.

Drug	References	No of patients	Dose (mg/m^2)	Infusion time	Terminal half-life[b], $t_{1/2}$	Residual[e] plasma[f]/blood[g] concentration (ng/ml)	Comment
Cisplatin[a]	Watanabe *et al.*, 2003	3	80	30 min	0.70±0.22 h	Day 2 - 14: below detection limit[f]	For patients with normal renal function
	Schellens *et al.*, 1996	45	70, 80		38 ± 10 min , (23 – 72) min		
	Delord *et al.*, 2009	11	100	1h	Cycle 1: 0.865± 0.198 h Cycle 2: 0.777 ±0.150 h Cycle 3: 0.756± 0.058		Pharmacokinetic parameters not statistically different amongst the 3 cycles
	Vermorken *et al.*, 1986	11	60-100	6 min-24 h	(26.0 - 78.8) min		
Docetaxel	Felici *et al.*, 2006	9	75	1 h	11.7± 7.1 h (4.0–24.0) h		
	Baker *et al.*, 2004	9	75	1.04± 0.036h [b]	17.5 ± 7.3 h[c] 91.7±32.1[d]	Day 22: 0.47±0.08 (~0.02% of C_{max})[f]	Concentrations on day 22 were below the lower limit of quantitation in 5 of 9 patients
	Brunsvig *et al.*, 2007	19	100	1h	18 (9-52)		The median ratio for AUCs of the second to the first cycle was close to 1
Gemcitabine	de Lange *et al.*, 2005	14	1000	30 min	11-26 min	Day 8: 0 [f]	No drug accumulation (weekly administration) C_{max} observed at the end of the infusion
	Fan *et al.*, 2010	7	1250	30 min	Day 1: 0.42± 0.20 h Day 5:0.67± 0.31 h	Day 5: 0 [f]	Pharmacokinetic parameters not statistically different between first (day 1) and second (day 5) dose administration
	Gan *et al.* 2006	9	1250	30 min	11±4 min		
Vinorelbine	Khayat *et al.*, 2004	18	30	20 min	32.0 ± 14.2 h	Day 3: ~ 3.6 (~0.35% of C_{max}) [g]	
	Lush *et al.*, 2005	24	30	20 min	49.13±10.04 h (36.07–73.38)	Day 8: ~0.6 (~0.03% of C_{max}) [g]	
	Delord *et al.*, 2009	11	60	oral			Pharmacokinetic parameters not statistical different between day 1 and day 8 of vinorelbine administration in the same cycle, or between the 3 cycles

[a] pharmacologically active unbound form of cisplatin in plasma, [b] Data represent mean ± SD (range), [c] Based on sampling up to 24h post-treatment, [d] Based on extended sampling up to 22 days post-treatment, [e] Drug administration takes place in day 1, C_{max}: maximum plasma concentration, AUC: Area under the plasma concentration vs. time curve

Table B. Pharmacodynamic properties of cisplatin, docetaxel, gemcitabine and vinorelbine.

Drug	Onset of apoptosis after treatment	References
Cisplatin	96h	Sorenson *et al.*, 1990
Docetaxel	24-48 h	Fabbri *et al.*, 2006; Fabbri *et al.*, 2008
Gemcitabine	0-48 h	Cappella *et al.*, 2001
Vinorelbine	~ 8 h	Aggarwal *et al.*, 2008

Table C. Comparison of time scales

Drug	Dosage interval, τ_D (days)	Interval between last administration and final CT acquisition, τ_A (days)	Typical terminal half-life, $t_{1/2}$ (hours)	$\tau_D/t_{1/2}$	$\tau_A/t_{1/2}$
Cisplatin	21-35	19-28 (one patient 7)	0.7	>720	>240
Docetaxel	21	19	17	30	27
Gemcitabine	Same cycle:7-8 Between cycles:14	12-14	0.4	Same cycle:>420 Between cycles: 840	>720
Vinorelbine	Same cycle:7 Between cycles:14-28	13-21 (one patient 7)	40	Same cycle:4.2 Between cycles:8.4-16.8	12.6 (4.2)

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