Supplementary material

Interface model

The interface model is a nonlinear effect-compartmental model in which the elimination mechanism is controlled by the state variable $y(t)$ (Meille *et al*, 2008). This latter variable represents the effect of the drug and is related to the drug plasma concentration $c(t)$ as follows:

$$\frac{dy}{dt} = -\alpha \exp(-\beta y) y + (c - \gamma) H(c - \gamma)$$

with an initial condition $y(0) = 0$. Here, α, β and γ are constants, and H is the Heaviside function, i.e., $H(x) = 1$ for $x \geq 0$ and 0 otherwise. Parameters α and β control the shape of the output $y(t)$. Parameter γ is a threshold parameter with adjustment for the input $c(t)$. In the case with $\alpha = 0$ and $\gamma = 0$, the interface model coincides with the area under the curve model.

PK

The first five equations of the model represent the pharmacokinetic models for etoposide and cisplatin. Etoposide kinetics are usually described by a model with two compartments that have elimination in the central compartment (Tranchand *et al*, 1999). The equations are:

$$\frac{dc_1}{dt} = -(k_e + k_{12})c_1 + k_{12}c_2 + \frac{u_1(t)}{V_1}$$
$$\frac{dc_2}{dt} = k_{21}(c_1 - c_2)$$

where c_1 and c_2 represent the etoposide concentrations in the central and peripheral compartments, respectively. For cisplatin, we use a three-compartment model (Monjanel-Mouterde *et al*, 2003):

$$\frac{dc_3}{dt} = -(k_e + k_{12} + k_{13})c_3 + k_{12}c_4 + k_{13}c_5 + \frac{u_2(t)}{V_1}$$
$$\frac{dc_4}{dt} = k_{21}(c_3 - c_4)$$
$$\frac{dc_5}{dt} = k_{31}(c_3 - c_5)$$

where c_3, c_4 and c_5 represent the concentrations in the central compartment and the second and third compartments, respectively. Parameter values are given in Table 8.

Interfaces

A particularity of our model is that there is an interface-type model related to the neutrophils, platelets and tumour volume for each drug.

Equations of the ANC interface model are as follows:

$$\frac{dy_1}{dt} = -\alpha_1 \exp(-\beta_1 y_1) y_1 + (c_1 - \gamma_1) H(c_1 - \gamma_1)$$
$$\frac{dy_2}{dt} = -\alpha_2 \exp(-\beta_2 y_2) y_2 + (c_3 - \gamma_2) H(c_3 - \gamma_2),$$

where y_1 and y_2 represent the ANC interface variables for etoposide and cisplatin, respectively.

Equations of the PLT interface model are:

37
$$\frac{dy_3}{dt} = -\alpha_3 \exp(-\beta_3 y_3) y_3 + (c_1 - \gamma_3) H(c_1 - \gamma_3)$$
$$\frac{dy_4}{dt} = -\alpha_4 \exp(-\beta_4 y_4) y_4 + (c_3 - \gamma_4) H(c_3 - \gamma_4),$$

38 where y_3 and y_4 represent the PLT interface variables of etoposide and cisplatin, respectively.

39 Equations of the tumour interface model are:

40
$$\frac{dy_5}{dt} = -\alpha_5 \exp(-\beta_5 y_5) y_5 + (c_1 - \gamma_5) H(c_1 - \gamma_5)$$
$$\frac{dy_6}{dt} = -\alpha_6 \exp(-\beta_6 y_6) y_6 + (c_3 - \gamma_6) H(c_3 - \gamma_6).$$

41 Similarly, here y_5 and y_6 represent the tumour regression interface variables for etoposide and

42 cisplatin, respectively. The parameter values are given in Table 9.

43

44 **Haemotoxicity model**

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46 We consider a simple, physiologically realistic model for haematopoiesis to describe the

47 dynamics of neutrophils and platelets. We assume that the production rate of progenitor cells

48 u is regulated by a homeostatic feedback mechanism controlled by the mature neutrophils w.

49 Due to maturation and replication in the haematopoietic chain, progenitors control the

50 production of mature neutrophils after a time delay, τ. This process is described by the

51 following equations:

52
$$\frac{du}{dt} = k_u \operatorname{Re} g - (k_u + N) u$$
$$\frac{dw}{dt} = \delta u(t - \tau) - k_w w,$$

53 with $\delta = k_w w_0$. The constants k_u and k_w are associated with natural elimination of neutrophils

and progenitors. $\mathrm{Re}\, g$ represents the neutrophil-mediated regulation of the progenitors via cytokines. We considered

$$\mathrm{Re}\, g = \left(\frac{w_0}{w} \right)^{\phi},$$

where w_0 is the standard number of neutrophils without the effect of drugs, and ϕ is a positive constant. N represents the cytotoxic effect of both drugs. We set

$$N = \alpha y_1 + \beta y_2$$

where parameters α and β are associated with the effects of etoposide and cisplatin, respectively.

Similarly, for the platelets, we used the following equations:

$$\begin{aligned} \frac{dv}{dt} &= k_v\, \mathrm{Re}\, g_1 - (k_v + N_1)u \\ \frac{dp}{dt} &= \delta_1 v(t - \tau_1) - k_p p, \end{aligned}$$

with $\delta_1 = k_p p_0$, $\mathrm{Re}\, g_1 = (p_0 / p)^{\phi_1}$ and $N_1 = \alpha_1 y_3 + \beta_1 y_4$. The parameter values are given in Table 10.

Modelling tumour growth

Several studies have shown that the Gompertz model reproduces significant tumour growth. In our model, we used a Gompertz type growth that is described by the following equation:

$$\frac{dn}{dt} = \lambda \log\left(\frac{M}{n} \right) n - Kn.$$

In this latter equation, n represents the number of cancer cells, M is a carrying capacity or the

maximal number of cells that can be attained and K represents the cytotoxic effects of both drugs. Letting $K = 0$ means that there is no treatment. We set the initial tumour mass equal to 30 g, such that $n(0) = 30$ and M = 1000 g, which is equivalent to 10^{12} cells. The coefficient λ was chosen such that the doubling time is equal to 30 days, which corresponds to the observed doubling time for SCLC (Hasegawa *et al*, 2000; Al-Ajam *et al*, 2005; Harris *et al*, 2012). We set

$$K = e_{eto} y_5 + e_{cis} y_6 + 2 \cdot syn \cdot \sqrt{(e_{eto} y_5)(e_{cis} y_6)}$$

where e_{eto} and e_{cis} are two constants that calibrate the cytotoxic effects of etoposide and cisplatin, respectively. Finally, syn is a synergy coefficient between the two drugs. Parameter values are given in Table 11.

Bibliography

Al-Ajam M, Seymour A, Mooty M, Leaf A (2005) Ten years of disease-free survival between two diagnoses of small-cell lung cancer: a case report and a literature review. *Med Oncol Northwood Lond Engl* **22**: 89–97, doi:10.1385/MO:22:1:089.

Harris K, Khachaturova I, Azab B, Maniatis T, Murukutla S, Chalhoub M, Hatoum H, Kilkenny T, Elsayegh D, Maroun R, Alkaied H (2012) Small cell lung cancer doubling time and its effect on clinical presentation: a concise review. *Clin Med Insights Oncol* **6**: 199–203, doi:10.4137/CMO.S9633.

Hasegawa M, Sone S, Takashima S, Li F, Yang ZG, Maruyama Y, Watanabe T (2000) Growth rate of small lung cancers detected on mass CT screening. *Br J Radiol* **73**: 1252–1259, doi:10.1259/bjr.73.876.11205667.

Meille C, Iliadis A, Barbolosi D, Frances N, Freyer G (2008) An interface model for dosage adjustment connects hematotoxicity to pharmacokinetics. *J Pharmacokinet Pharmacodyn* **35**: 619–633, doi:10.1007/s10928-008-9106-4.

Monjanel-Mouterde S, Ciccolini J, Bagarry D, Zonta-David M, Duffaud F, Favre R, Durand A (2003) Population pharmacokinetics of cisplatin after 120-h infusion: application to routine adaptive control with feedback. *J Clin Pharm Ther* **28**: 109–116.

Tranchand B, Amsellem C, Chatelut E, Freyer G, Iliadis A, Ligneau B, Trillet-Lenoir V, Canal P, Lochon I, Ardiet CJ (1999) A limited-sampling strategy for estimation of etoposide pharmacokinetics in cancer patients. *Cancer Chemother Pharmacol* **43**: 316–322, doi:10.1007/s002800050901.