

A new protocol for the administration of etoposide and cisplatin in extensive-stage small-cell lung cancer patients

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Objectives

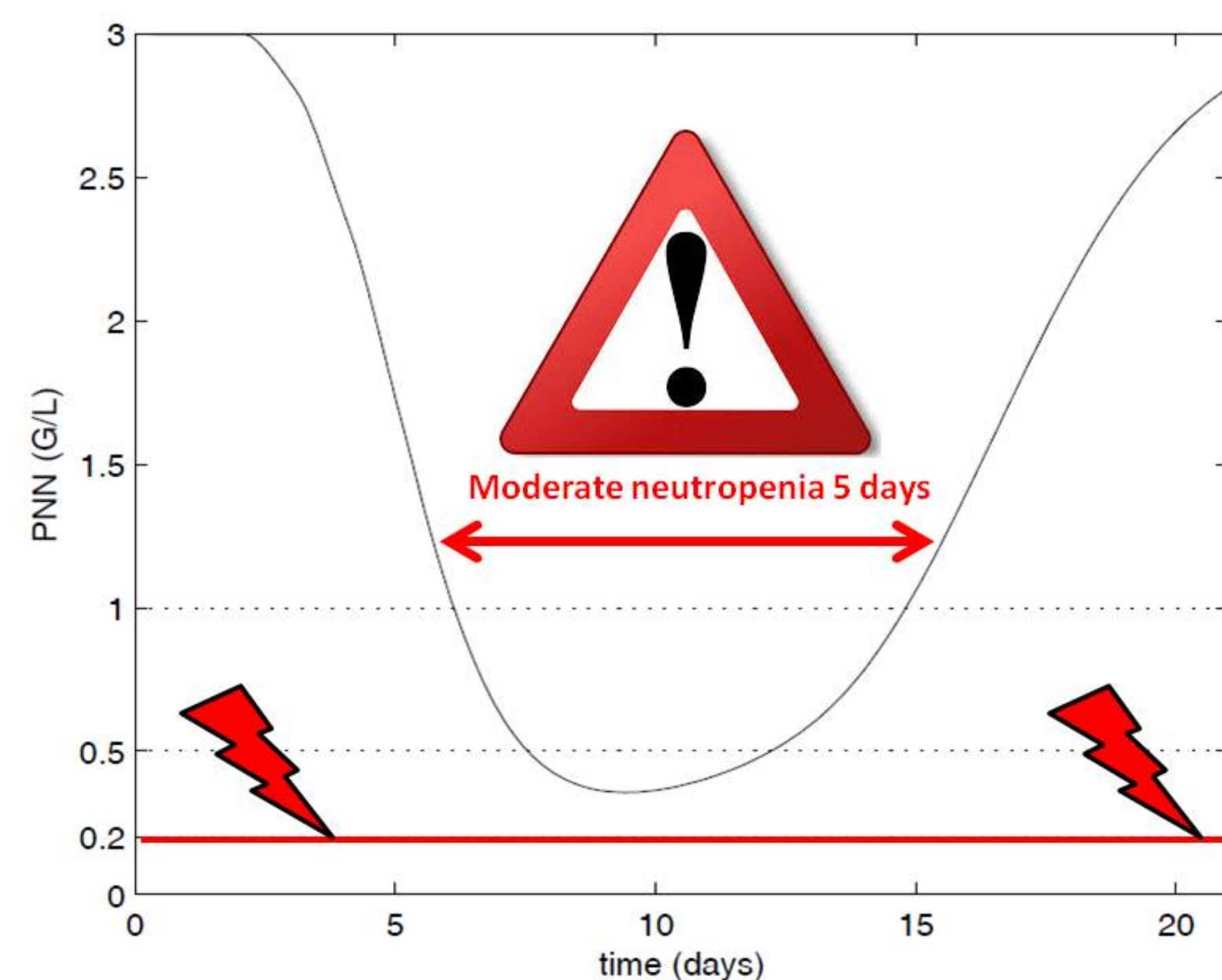
Finding new optimized protocols

- Achieving **better tumor regression** compared to standard protocols
- Respecting **toxicity constraints** Neutropenia & Thrombopenia

Background



- SCLC represent 20% of lung cancer, which is the leading cause of cancer death in the world
- Important sensitivity of SCLC to chemotherapy and radiotherapy
- Standard treatment protocols: bad survival rates and life-threatening cytotoxic effects



Materials

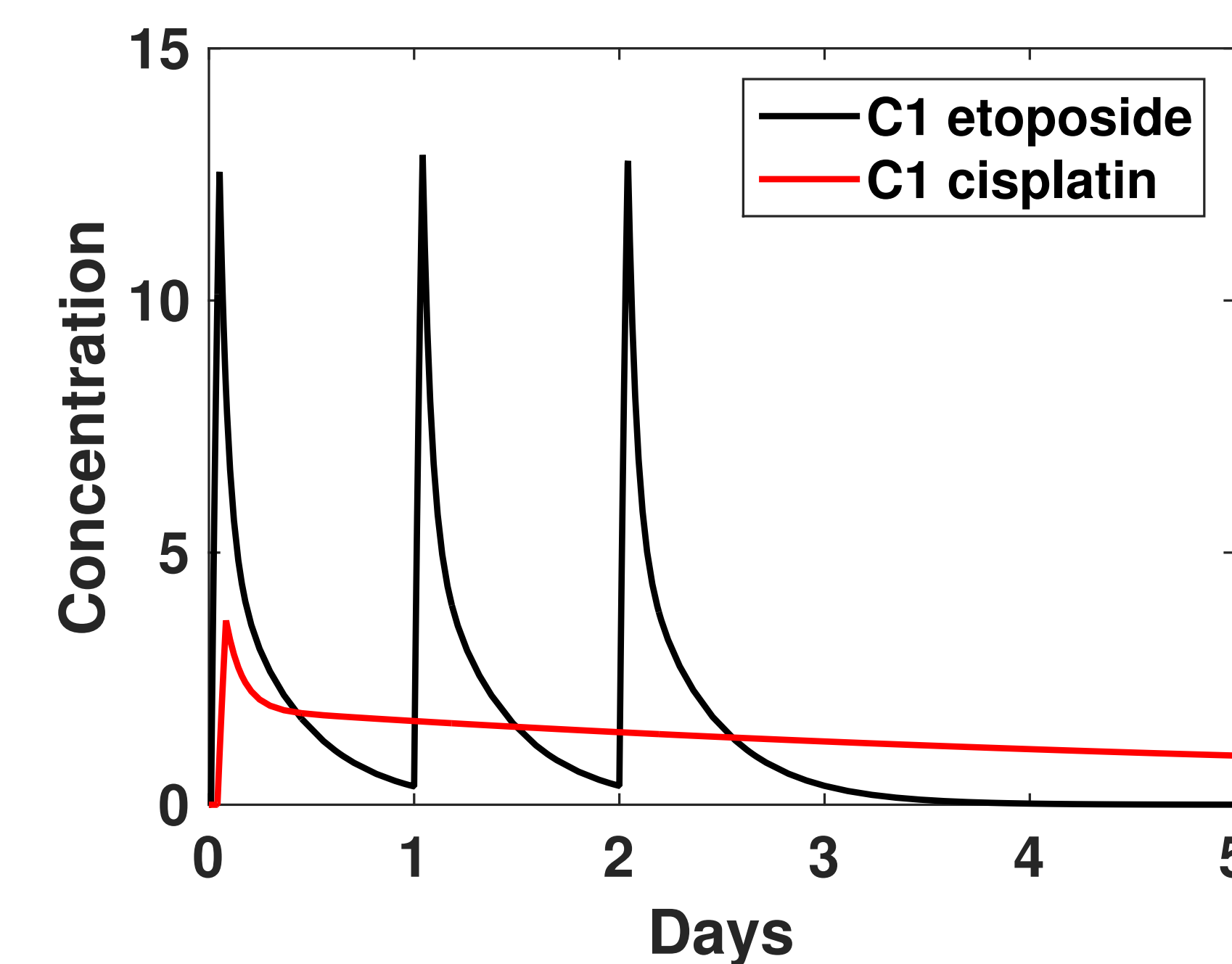
- PK/PD mathematical model for etoposide-cisplatin combination [1, 2]
- Parameters are adjusted to be in concordance with previous studies



Methods

- Optimal doses and schedules

$$\mathbf{d}^* = \operatorname{argmin} \left\{ \frac{1}{T} \int_0^T z(t, \mathbf{d}, \mathbf{t}^*) \right\}$$



Important Results

Optimized protocol 1

etoposide: 80mg/m² 0h-1h, followed 12h later by a long infusion (3 days) of 160mg/m².
cisplatin: 80mg/m² 1h-2h.

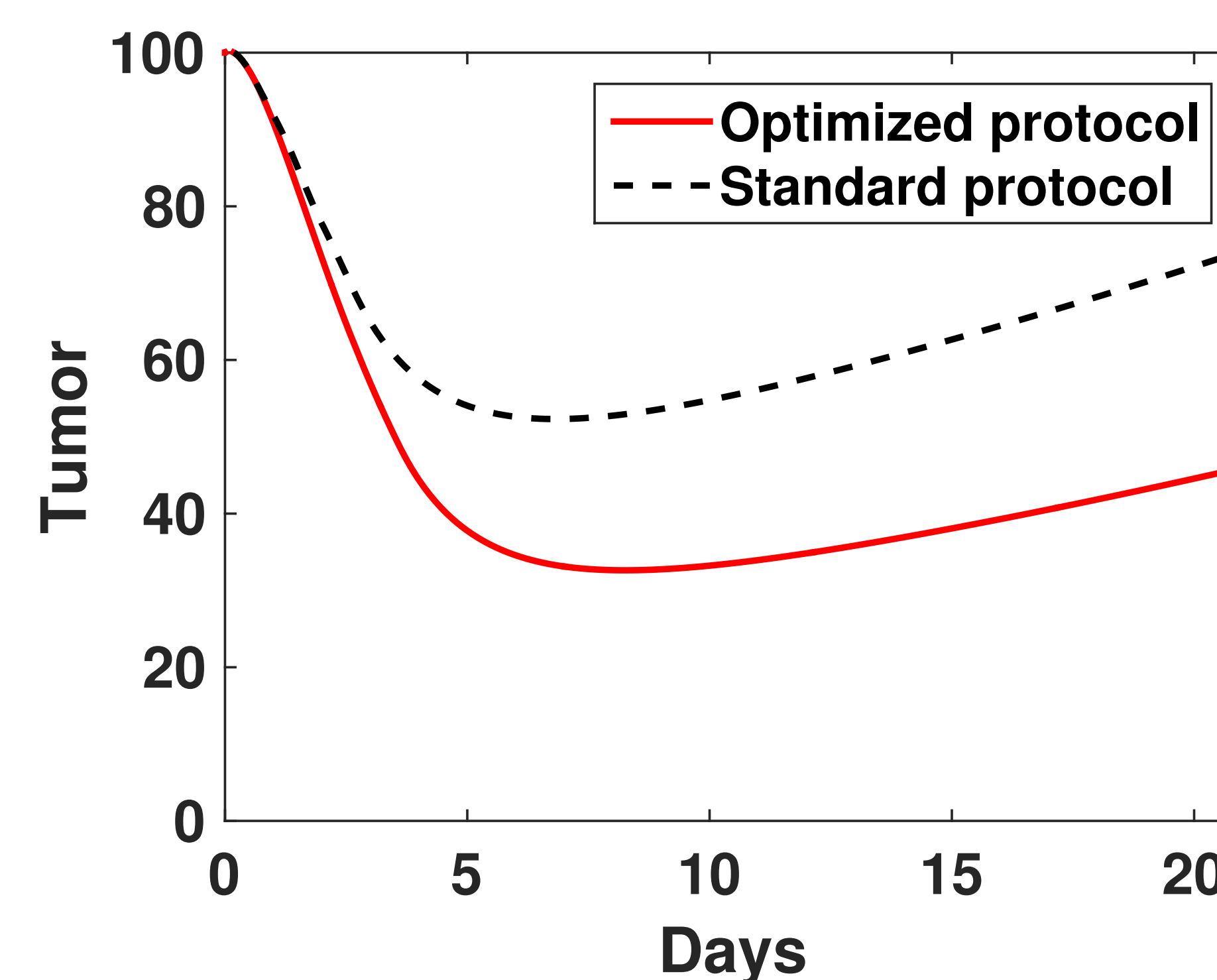
Optimized protocol 2 (high dose)

etoposide: 80mg/m² 0h-1h, followed 12h later by a long infusion (4 days) of 300mg/m².
cisplatin 100mg/m² 1h-2h.

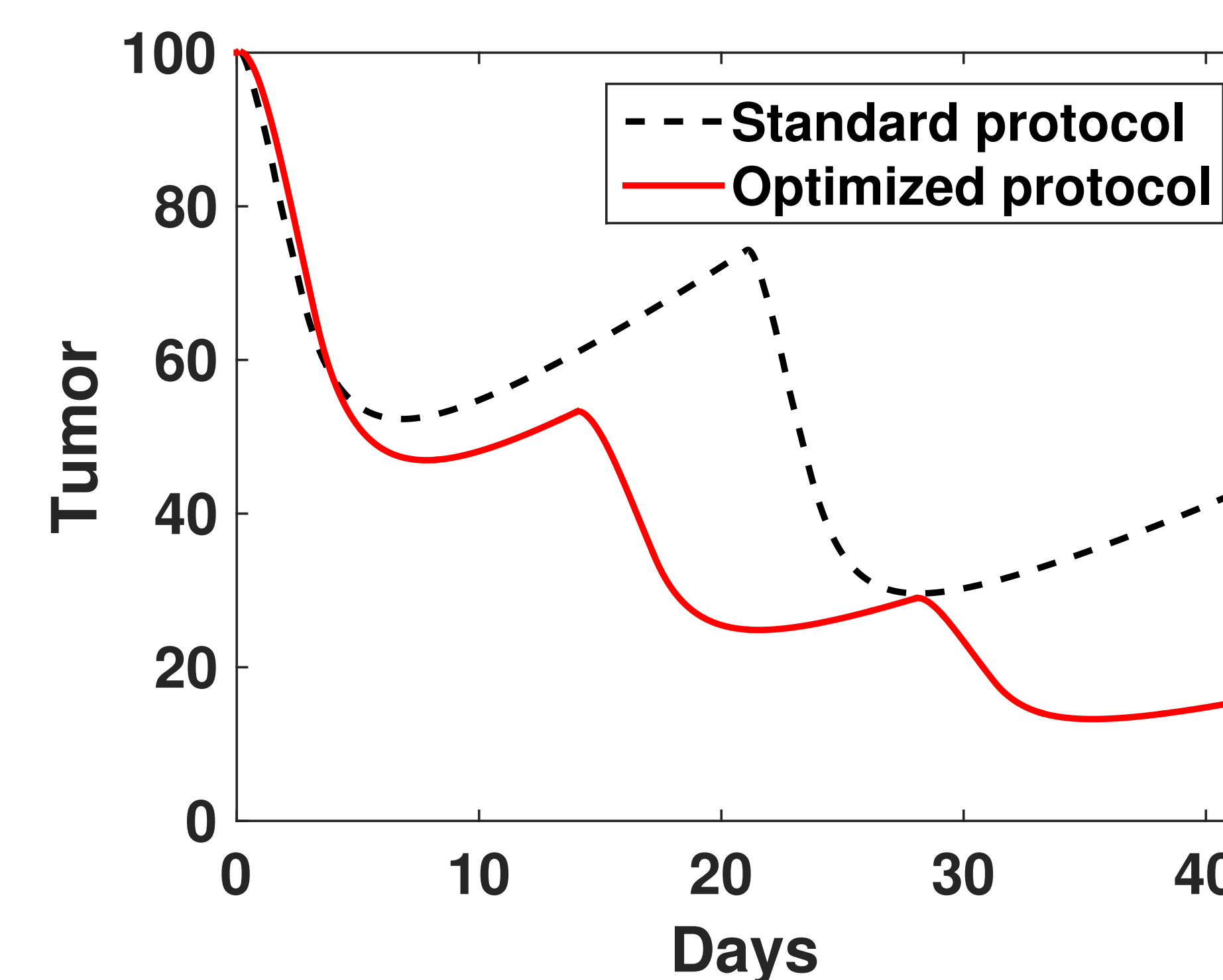
Optimized protocol 3 (intensified, cycles of 14 days)

etoposide: 40mg/m² 0h-1h, followed 6h later by a long infusion (3 days) of 105mg/m².
cisplatin: 50mg/m² 1h-2h.

OP1 Vs Standard protocol [3]



OP3 Vs Intensified protocol [3]



Mathematical model (concept)

- PK component: two compartment models

$$\begin{aligned} \dot{c}_1 &= -k_e c_1(t) + \sum_{s=2}^L k_{1s} (c_1(t) - c_s(t)) + \frac{u(t)}{V_1} \\ \dot{c}_s &= k_{s1} (c_1(t) - c_s(t)) \end{aligned}$$

- Interface component

$$\dot{y} = -\alpha \exp(-\beta y) y + (c_1 - \gamma) H(c_1 - \gamma)$$

- PD component: neutrophils and platelets dynamics

$$\begin{aligned} \dot{u} &= k_u \operatorname{Reg} - (k_u + f(y)) u \\ \dot{w} &= \delta u(t - \tau) - k_w w \end{aligned}$$

- Tumor growth component

$$\dot{z} = \lambda \log \left(\frac{M}{z} \right) z - g(y) z$$

References

- C. Meille et al. Revisiting dosing regimen using pharmacokinetic/pharmacodynamic mathematical modeling: Densification and intensification of combination cancer therapy. *Clinical Pharmacokinetics*, pages 1–11, 2016.
- E. Hénin et al. Revisiting dosing regimen using pk/pd modeling: the model1 phase i/ii trial of docetaxel plus epirubicin in metastatic breast cancer patients. *Breast Cancer Research and Treatment*, 156(2):331–341, 2016.
- D C. Ihde et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *Journal of Clinical Oncology*, 12(10):2022–34, 1994.

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