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# Mathematical optimisation of the cisplatin plus etoposide combination for managing extensive-stage small-cell lung cancer patients

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**Background:** Small-cell lung cancer (SCLC) represents one of the most aggressive forms of lung cancer. Despite the fair sensitivity of SCLC to chemotherapy and radiotherapy, the current standard treatment regimens have modest survival rates and are associated with potential life-threatening adverse events. Therefore, research into new optimised regimens that increase drug efficacy while respecting toxicity constraints is of primary importance.

**Methods:** A PK/PD model for the combination of cisplatin and etoposide to treat extensive-stage SCLC patients was generated. The model takes into consideration both the efficacy of the drugs and their haematological toxicity. Using optimisation techniques, the model can be used to propose new regimens.

**Results:** Three new regimens with varying timing for combining cisplatin and etoposide have been generated that respect haematological toxicity constraints and achieve better or similar tumour regression. The proposed regimens are: (1) Protocol OP1: etoposide 80 mg m$^{-2}$ over 1 h D1, followed by a long infusion 12 h later (over 3 days) of 160 mg m$^{-2}$ plus cisplatin 80 mg m$^{-2}$ over 1 h D1, D1–D1 21 days; (2) Protocol OP2: etoposide 80 mg m$^{-2}$ over 1 h D1, followed by a long infusion 12 h later (over 4 days) of 300 mg m$^{-2}$ plus cisplatin 100 mg m$^{-2}$ over 1 h D1, D1–D1 21 days; and (3) Protocol OP3: etoposide 40 mg m$^{-2}$ over 1 h, followed by a long infusion 6 h later (3 days) of 105 mg m$^{-2}$ plus cisplatin 50 mg m$^{-2}$ over 1 h, D1–D1 14 days.

**Conclusions:** Mathematical modelling can help optimise the design of new cisplatin plus etoposide regimens for managing extensive-stage SCLC patients.

Lung cancer is the leading cause of cancer death worldwide. Among the different lung cancer subtypes, small-cell lung cancer (SCLC) accounts for 15 to 20% of cases. The SCLC is characterised by an important metastatic-spread ability and a 60 to 80% response rate to chemotherapy ± radiotherapy. Despite these high response rates, the median overall survival (OS) remains short (~10 months) that is mainly because of distant relapses. To date, the most commonly used chemotherapy regimen is based on the combination of cisplatin (75 mg m$^{-2}$ on day 1) or carboplatin (with a dose calculated using Calvert or Chatelut formulas) plus etoposide (120 mg m$^{-2}$ on days 1 to 3) for 4 to 6 cycles (Evans *et al*, 1984; Porter *et al*, 1985; Calvert *et al*, 1989; Chatelut *et al*, 1995). Other regimens are less commonly used (Bunn *et al*, 1986; Fukuoka *et al*, 1991; Roth *et al*, 1992; Trillet-Lenoir *et al*, 1993; Sculier *et al*, 1998). The safety profile of these combinations is characterised by haematological (neutropenia and

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thrombocytopenia) and extra-haematological (nausea and vomiting, renal, peripheral neuropathy and alopecia) adverse events. Therefore, further research progress is needed.

Several studies have shown that changes in the doses and schedules of widely used regimens might lead to improved efficacy and tolerability (Gurney *et al*, 1991; van Warmerdam *et al*, 1997; Freyer *et al*, 2001; Moore *et al*, 2006). Could this be the case for SCLC regimens? As an example, the importance of scheduling etoposide administration was shown in a study by Slevin *et al* (1989). The authors compared two distinct protocols (etoposide 500 mg m$^{-2}$ over 24 h at D1 *vs* 100 mg m$^{-2}$ over 2 h from D1 to D5) for chemo-naive patients with stage IV SCLC. Surprisingly, the ORR increased from 10% to 90% for the two modalities. Although all patients were given the same total dose, and the average area under the curve (AUC) was comparable for all patients, the times during which the blood concentration of etoposide stayed above 1 mg l$^{-1}$ were 46 and 94 h, respectively. Concomitantly, several studies suggested that intensive regimens could have better response and survival rates with an increase in the toxicity, making these regimens difficult to use in practice (Cohen *et al*, 1977; Tourani *et al*, 1993, 2000). Is there room for improvement of our currently used cisplatin plus etoposide regimen? Because of the multitude of possibilities, empirical approaches are impractical and impossible to test. As a result, mathematical modelling is needed.

There are several approaches to model tumour regression while keeping drug toxicity effects below an acceptable level. In most of these approaches, however, it is difficult to efficiently control the toxicity constraints. Recently, in a convincing study, Meille and colleagues (Hénin *et al*, 2016; Meille *et al*, 2016) developed a mathematical model to optimise drug dosing regimens and redesign the dose intensification–dose escalation process with intensified cycles of combined anticancer drugs. As for the work by Meille and colleagues (Hénin *et al*, 2016; Meille *et al*, 2016), we propose a PK/PD mathematical model in this study for approaching the combination of cisplatin and etoposide to treat extensive-stage SCLC patients. The aim was to determine optimised temporal protocols that can minimise the tumour mass while avoiding harmful toxic side effects, namely severe neutropenia and thrombocytopenia.

## MATERIALS AND METHODS

**Mathematical model.** The model assessed the combination of cisplatin and etoposide by evaluating both haematological toxicities (neutropenia and thrombocytopenia) and changes in the tumour volume. The model is mainly divided into three components (Meille *et al*, 2016). One is a PK component that describes the pharmacokinetics of cisplatin and etoposide (see Supplemental Material, section PK). This component consists of a two-compartment model for etoposide (Tranchand *et al*, 1999) and a three-compartment model for cisplatin (Monjanel-Mouterde *et al*, 2003). A PD-safety component consists of two systems of differential equations describing the changes in neutrophil and platelet counts and a PD-efficacy component describing the changes in the tumour volume (see Supplemental Material, sections Hematoxicity model and Modelling tumor growth). A fundamental problem in PK/PD modelling is the PK/PD link. To circumvent this difficulty, we used an adequate exposure model (labelled the 'interface model' by the authors who proposed this concept) that can be considered a generalisation of both the AUC and the effect compartment model (Meille *et al*, 2008; see Supplementary Material sections Interface model and Interfaces).

To assess the validity of our model, simulation results were compared with the results of published clinical studies from the literature that assessed the cisplatin and etoposide combination for extensive SCLC patient management (Slevin *et al*, 1989; Ihde *et al*, 1994).

**Toxicity constraints.** The model was subject to three constraints in the risk of haematological adverse events. First, the model requires that the neutrophil and platelet counts permanently stay above an absolute threshold level (that is, $w(t) \geqslant w_{abs}$ at any time $t$, with $w_{abs} = 0.2$ g l$^{-1}$ and $p(t) \geqslant p_{abs}$ at any time $t$ and $p_{abs} = 20$ g l$^{-1}$). Second, the model requires that the times ($t_{wrel}$ and $t_{prel}$) for which neutrophil and platelet counts are between defined threshold levels ($w_{rel}$ and $p_{rel}$) and the absolute threshold wabs, should not exceed predefined lengths of time (with $w_{rel} = 1$ g l$^{-1}$, $p_{rel} = 50$ g l$^{-1}$, $t_{wrel} = 3$ days and $t_{prel} = 3$ days). Third, the model requires haematological recovery at the time of the subsequent treatment cycle, with neutrophil and platelet counts that are above predefined threshold values ($w_{rec} = 2$ g l$^{-1}$ and $p_{rec} = 150$ g l$^{-1}$). Erythropenia is also an important aspect. However, it rarely leads to treatment delay or interruption as it could be managed red blood transfusions and/or EPO-stimulating agents. Therefore, it would be preferable to not overload the model with additional equations and parameters by incorporating another toxicity constraint.

**Optimisation of the cisplatin plus etoposide regimen.** The optimisation procedure can be considered as finding a temporal distribution for the drug doses that achieve the best efficacy while respecting toxicity constraints for a particular patient (using the model). The problem can be described as finding a schedule $\underline{s}^{opt}$ and distribution of doses $\underline{d}^{opt}$, such that the average value of the tumour size over an entire cycle $\frac{1}{T}\int_0^T n(t;\underline{s},\underline{d})dt$ is minimal and the aforementioned toxicity constraints not violated. Our choice of minimising the integral of $n$ rather than its value at the end of the cycle is based on the Goldie–Coldman hypothesis (Coldman and Goldie, 1983). This hypothesis suggests that the probability that a cancer would contain drug-resistant clones depends on the mutation rate and the size of the tumour. Therefore, we aimed at minimising the tumour size as much as possible during a cycle to avoid acquired resistance. This implies that we targeted the minimal size that can be reached in order to decrease the chances of developing resistant clones.

## RESULTS

**Model validation.** The model includes a large number of parameters that are usually individual dependent and thus vary from one patient to another, especially the pharmacokinetic parameters of cisplatin and etoposide. Because not all necessary clinical data from stage IV SCLC patients were available, a standard pharmacokinetic population fit approach could not be performed. To circumvent this issue, parameters were adjusted such that our simulations fit with the clinical results in the literature. Therefore, we searched for a set of parameters following a log-normal distribution that achieved, for a standard treatment, tumour regression and haematologic profiles that were similar to the results reported in the literature. As an example, we first tested the validity of the model using the results from Slevin *et al* (1989). We assessed the outcomes for 1000 'virtual' patients (each patient has a distinct set of parameters drawn from a log-normal distribution with the same mean and s.d. values for all patients)

**Table 1. Comparison of the overall response rate between the model and clinical results after 6 cycles of protocols proposed by Slevin *et al* (1989)**

| Protocol | Slevin *et al* (1989) | Model | 95% CI |
|---|---|---|---|
| 500 mg m$^{-2}$ D1 | 10% | 8% | (11–36%) |
| 100 mg m$^{-2}$ D1–D5 | 90% | 91% | (74–95%) |

Abbreviations: CI = confidence interval; D, day.

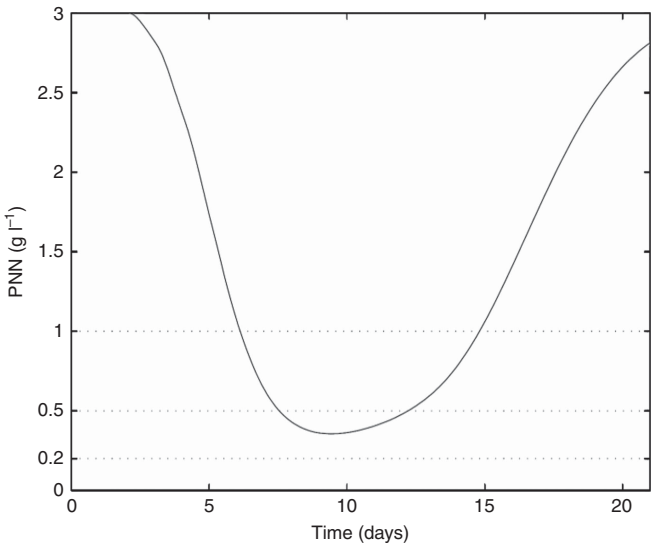


Figure 1. Absolute neutrophil count (ANC) profile using the high dose protocol by Ihde *et al* (1994).

**Table 2. Comparison of the response rate between the model and clinical results after 4 cycles of the EP protocol (Ihde *et al*, 1994)**

| Response | Ihde *et al* (1994) | Model | 95% CI |
|---|---|---|---|
| Complete | 22% | 25% | (11–36%) |
| Partial + complete | 83% | 85% | (74–95%) |

Abbreviations: CI = confidence interval; EP=etoposide/cisplatin.

**Table 3. Summary of the optimised protocols proposed by the model**

| | Etoposide | | Cisplatin | |
|---|---|---|---|---|
| Protocol | Time | Dose | Time | Dose |
| OP1 | 0–1 h<br>12–84 h | 80 mg m$^{-2}$<br>160 mg m$^{-2}$ | 1–2 h | 80 mg m$^{-2}$ |
| OP2 (intensified) | 0–1 h<br>12–108 h | 80 mg m$^{-2}$<br>300 mg m$^{-2}$ | 1–2 h | 80 mg m$^{-2}$ |
| OP3 (14-day cycle) | 0–1 h<br>6–78 h | 40 mg m$^{-2}$<br>105 mg m$^{-2}$ | 1–2 h | 50 mg m$^{-2}$ |

over 6 cycles to mimic a clinical study. The results reported in Table 1 showed a good correlation between the model and the reported clinical data. Then, we tested the model validity using the results from Ihde *et al* (1994). Using the model, grade 4 neutropenia over 5 days (Figure 1) was observed that is in line with the study results. Therefore, the model confirmed severe haematological toxicity using this regimen. Furthermore, the comparison of the response rate outcomes between our model and the results reported by Ihde *et al* (1994) were in agreement (Table 2). Additional results given in Supplementary Tables 4–7 showed a good correlation between the model and the reported clinical data for both the etoposide/cisplatin (EP) and intensified EP regimens.

**Improved standard regimen: OP1 regimen (focussing on response).** This optimised regimen should have the same characteristics of the EP protocol, that is: (1) a maximal total dose for etoposide equal to 240 mg m$^{-2}$ and (2) a maximal total dose for cisplatin equal to 80 mg m$^{-2}$ per cycle. The model suggested a new infusion schedule for etoposide, with a short infusion of 80 mg m$^{-2}$ followed by a long infusion of 160 mg m$^{-2}$ 12 h later over 3 days. Cisplatin (80 mg m$^{-2}$) was infused for 1 h after the first etoposide infusion (Table 3). The model suggests that the timing of cisplatin infusion does not affect the optimised regimen and that cisplatin can be administered at any time during day 1. Compared with the standard EP protocol, the OP1 regimen yielded better tumour regression, with a response rate of 50% instead of 30% after one treatment cycle (Figure 2). Simulations for 1000 patients led to a response rate of 98% for the OP1 *vs* 85% for the EP after 4 treatment cycles. Moreover, the OP1 regimen was less toxic than the standard EP regimen as assessed by the ANC counts (data not shown).

**Improved high dose regimen: OP2 regimen.** The model demonstrated that the intensified EP protocol (etoposide 80 mg m$^{-2}$ J1–J5 and cisplatin 27 mg m$^{-2}$ J1–J5) did not fit with the predefined safety constraints. Indeed, the model showed that (for 2 cycles) the intensified EP protocol produced grade 3 neutropenia during 5 days that broke the predefined limit of 3 days for this toxicity. The model proposed an optimised regimen called the OP2 regimen (etoposide 80 mg m$^{-2}$ over 1 h on day 1 followed 1 h later by cisplatin 100 mg m$^{-2}$ over 1 h and then followed 12 h later by a prolonged infusion of 4 days of etoposide at a dose of 300 mg m$^{-2}$, Table 3). The OP2 regimen yielded a better tumour response than the high EP regimen (Figure 3) while respecting the haematological predefined constraints (grade 3 neutropenia for $<3$ days).

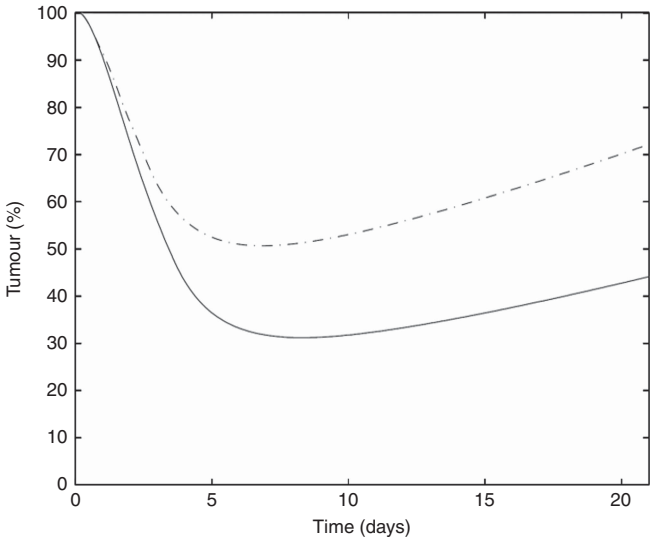


Figure 2. Comparison of tumour growth. Dashed line indicates standard protocol and solid line indicates optimised protocol OP1.

**Intensified EP regimen: OP3 regimen.** The model was set up to explore the possibility of an intensified EP regimen by reducing the cycle length (2 weeks instead of 3 weeks). The model assessed a regimen consisting of 3 cycles of 14 days compared with 2 cycles of the standard EP protocol. Using our model, optimisation led to a regimen called the OP3 regimen (Table 3). After 2 treatment cycles, the OP3 regimen led to a response rate of 80% compared with 60% for the standard EP protocol without violating the toxicity constraints (Figure 4).

## DISCUSSION

The SCLC patients still present with several unmet needs that are partially linked to the limited long-term efficacy and adverse event

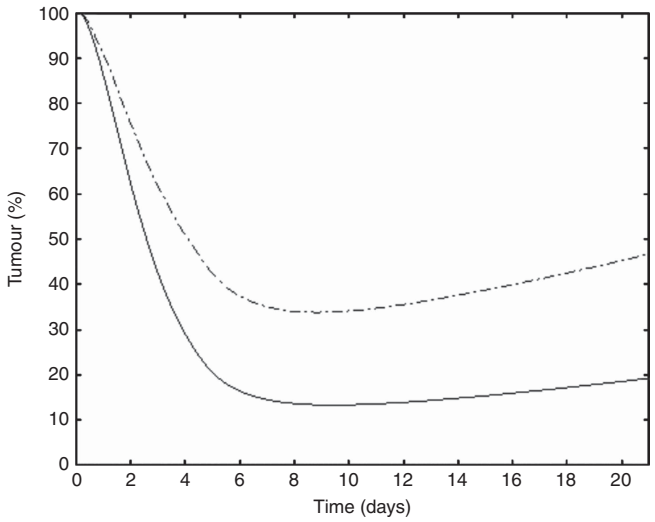


Figure 3. Comparison of tumour growth. Dashed line indicates high EP protocol and solid line indicates optimised protocol OP2.

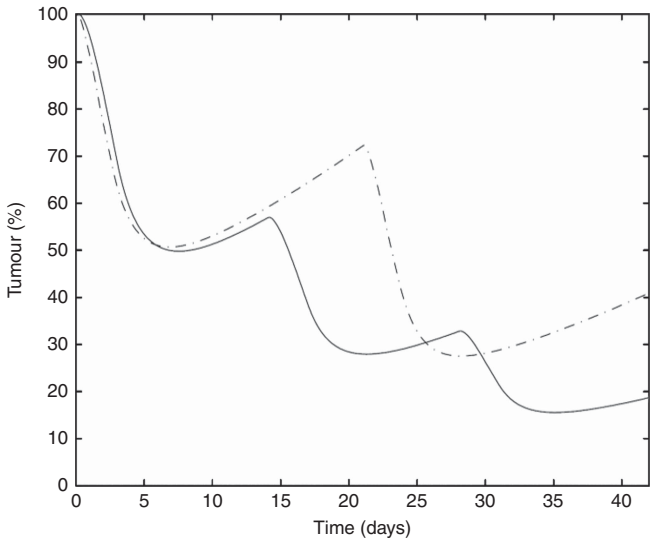


Figure 4. Comparison of tumour growth. Dashed line indicates standard protocol and solid line indicates intensified protocol OP3.

rate of the currently available standard cisplatin plus etoposide regimen. Intensifying strategies that increase the standard dose (Cohen *et al*, 1977; Tourani *et al*, 2000) or administer additional drugs (Pujol *et al*, 2001) yield slightly better OS, but they are more toxic. Modified schedules are more efficacious in some cases and are much worse in others (Slevin *et al*, 1989) without a rational understanding of the reason for this enormous difference. Improving the toxicity to efficacy balance of the etoposide plus cisplatin regimen is not empirically simple, as demonstrated by the relative failure of all newly proposed regimens.

The results reported here propose three newly optimised regimens based on mathematical modelling of the cisplatin plus etoposide combination. The mathematical modelling takes advantage of the many combinations that could be simultaneously tested *in silico* to propose regimens that provide the highest response rates while respecting the haematologic toxic constraints. The OP1 regimen involved adjustment of the temporal schedule of the standard regimen. The OP2 and OP3 regimens aimed to intensify the standard regimen by increasing the dose or reducing the cycle length. The model enabled the proposal of an optimised solution for all these situations with regimens that improve the expected response rate while respecting the constraints of the risk of haematological toxicity.

Two recent studies showed the benefits of using mathematical modelling to optimise dosing regimens. The first dealt with optimising metronomic oral vinorelbine in metastatic NSCLC and malignant pleural mesothelioma (Barbolosi *et al*, 2014; Bocci and Kerbel, 2016; Elharrar *et al*, 2016). A mathematical PK/PD model suggested an alternative weekly D1, D2 and D4 schedule with respective doses of 60, 30 and 60 mg that could lead to better safety and efficacy profiles. Currently, 12 patients are enrolled in a phase 1a study under the proposed optimised regimen, and the analysis has shown promising results. The second study focussed on redesigning the dose escalation process using densified cycles of combined docetaxel plus epiribucin anticancer therapy in metastatic breast cancer patients (Hénin *et al*, 2016; Meille *et al*, 2016). Using optimisation techniques, a mathematical model was developed to compute the total drug distribution for each escalation dose level and each drug in the combination. This enabled minimisation of the average tumour mass for each cycle while respecting predefined toxicity constraints.

One of the main drawbacks of the approach proposed in this study is the lack of clinical data that can weaken the model reliability. To circumvent this difficulty, we assessed the model validity by comparing its results with clinical study results taken from the literature. Our model results correlated well with the literature and suggest that it can be consolidated and used in clinical studies. Another issue with the modelling approach is its only indirect prediction of the OS. Indeed, the model cannot take into account the OS rate as a formal output of the optimisation procedure. This is inherent to the modelling structure as the input variables consist of pharmacokinetic and pharmacodynamic parameters. Therefore, the model can only address the relationship of these input parameters to output variables, such as haematological profiles and tumour volume regression, according to the RECIST. However, minimising toxicities while improving response rates might have the potential to produce better OS rates than standard protocols. This was proven in previous studies (Hénin *et al*, 2016; Meille *et al*, 2016) where the good management of toxicity constraints was associated to a doubling of the median overall survival. Nonetheless, this remains to be prospectively tested in a properly designed randomised study

The ultimate goal of this work is to establish a prospective phase I study in which patients are enrolled and treated according to the optimised regimens proposed in this study. During the first cycle, data samples measuring neutrophil and platelet counts, as well as drug concentrations, are collected for each patient and integrated into the model to recalibrate the parameters. Having data samples for each patient would allow for the use of Bayesian analysis to individualise treatments and propose patient-specific optimised regimens.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)