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# Validation of standard definition of *sensitive* versus *refractory* relapsed small cell lung cancer: A pooled analysis of topotecan second-line trials

Andrea Ardizzoni [a], Marcello Tiseo [a,*], Luca Boni [b]

[a] *Medical Oncology Unit, University Hospital, Parma, Italy*
[b] *Clinical Trials Coordinating Center, Istituto Toscano Tumori, University Hospital Careggi, Firenze, Italy*

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**Abstract** ***Background:*** Relapsed small cell lung cancer (SCLC) is classified into *sensitive* or *resistant* according to treatment-free interval (TFI) longer or shorter than 60 (criteria 1) or 90 (criteria 2) days. However, these criteria are based on small old studies and are inconsistent among different studies. The present study aimed at validating these criteria and assessing additional clinical parameters predictive of response rate (RR) and overall survival (OS).
***Patients and methods:*** A database of six GlaxoSmithKline-sponsored trials of intravenous topotecan-based second-line chemotherapy was analysed. Validation of *sensitive/resistant* definition was performed on the entire dataset (631 patients), while study of additional parameters and development of prognostic model was conducted dividing the database into derivation and validation sets.
***Results:*** The association between criterion 1 or 2 and RR was confirmed. Changing TFI cut-off or adding response to first-line did not improve accuracy. In addition to TFI ($P = 0.007$), only presence of liver metastasis ($P = 0.046$) was found to affect the probability of objective response. TFI, age, liver metastases, performance status (PS), albumin, haemoglobin and sodium levels were identified as independent prognostic factors for OS. A prognostic model, based on these variables, was able to separate relapsed SCLC into low versus high risk categories (median OS 41.4 versus 20.0 weeks).
***Conclusions:*** This study confirms the value of standard criteria for relapsed SCLC outcome prediction. Patients with TFI < 60 days are refractory to second-line chemotherapy and have poor OS. Patients with liver metastasis and/or PS2 and/or low albumin, regardless of TFI, have similarly poor outcome.


* *Corresponding author.* Address: Medical Oncology Unit, University Hospital of Parma, Via Gramsci 14, Parma 43125, Italy. Tel.: +39 0521 702316; fax: +39 0521 995448.
*E-mail address:* mtiseo@ao.pr.it (M. Tiseo).

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## 1. Introduction

Despite initial high sensitivity to chemotherapy, the majority of small cell lung cancer (SCLC) patients relapse or progress within few months [1–3]. Salvage chemotherapy has been found to yield modest quality of life and survival improvement [4,5].

A study assessing teniposide as second-line treatment of SCLC found a significantly higher probability of objective response (OR) for patients with a treatment-free interval (TFI) longer than 2.6 months [6]. The importance of TFI was further emphasised by studies indicating that patients with a longer TFI had a higher probability of achieving an OR to the same chemotherapy used in first-line (*rechallenge*) [7,8–11]. Thereafter, a distinction between *sensitive* patients, those with OR to first-line therapy and a TFI of at least 60 or 90 days, and *resistant*/*refractory* (from now on defined *resistant*) patients, those with no response to first-line or shorter TFI, has been adopted within the oncology community. However, this definition was designed many years ago based only on retrospective small series [6] when standard first-line was not yet platinum-based, and its validity has been put under discussion by some recent studies [12].

Moreover, different TFI cut-offs to distinguish between *sensitive* and *resistant* patients have been used in various pivotal studies. In the 090 trial (topotecan intravenous (i.v.) versus cyclophosphamide, doxorubicin and vincristine (CAV)) a 60-day cut-off was considered [13], whereas in the 396 trial (i.v. versus oral topotecan) a 90-day cut-off was used [14]. In addition, few trials included response to first-line as additional parameter to define *sensitive*/*resistant* category [14], as in the original definition [6] and in other studies with different agents [12,15].

The primary aim of this study was to validate the criteria currently used for defining *sensitive*/*resistant* relapsed SCLC by using the topotecan trials GlaxoSmithKline (GSK) database [16]. Secondly, we aimed at verifying whether a different temporal criterion and/or the addition of other clinical parameters could yield a better discrimination between *sensitive* and *resistant* categories of disease and, finally, we sought to assess the prognostic impact of *sensitive*/*resistant* categories and of other clinical factors on survival.

## 2. Patients and methods

### 2.1. Patients

Eligible patients had histological/cytological diagnosis of SCLC, with limited or extensive disease, recurrent or progressing during or after first-line chemotherapy who had received intravenous topotecan within prospective phase II–III studies [13,14,17–20]. Data retrieved from the GSK data-base included gender, age, performance status (PS), haemoglobin, albumin and sodium baseline levels, type of prior treatment, disease extension, sites of metastases and response to first-line chemotherapy.

Four classification criteria based on TFI and first-line OR were defined: criteria 1, TFI $<$ versus $\geqslant$ 60 days; criteria 2, TFI $<$ versus $\geqslant$ 90 days; criteria 3, TFI $<$ 60 days and/or lack of OR to first-line versus TFI $\geqslant$ 60 day and OR to first-line; criteria 4, TFI $<$ 90 days and/or lack of OR to first-line versus TFI $\geqslant$ 90 day and OR to first-line.

### 2.2. Statistical analysis

TFI was the interval from the last chemotherapy administration during first-line therapy and the occurrence of progressive disease.

To avoid the exclusion of cases with missing data, whose percentage was low ($<$1.3% of cases) with the exception of stage (16.8%) and albumin (8.6%), the multiple imputation method was used (10 imputations). Logistic regression and regression methods were used for imputation of categorical and continuous variables, respectively. Missing-at-random assumptions were made. Accuracy of classification criteria was investigated in 621 cases with complete raw data in terms of sensitivity, specificity, positive (PPV) and negative (NPV) predictive value, with their 95% confidence intervals (CIs).

In order to develop new prognostic criteria, the available dataset was divided, using a computer-generated random procedure, into derivation and validation sets, with an allocation ratio equal to 2:1.

Observation time of patients alive at the last follow-up visit was censored. Median follow-up time was estimated according to the Kaplan–Meier inverse method [21]. Firstly, the effect of each factor on OR and OS was analysed in a univariate setting, using logistic regression and Cox proportional hazards models, combining the results of the analyses of imputations. Multivariate logistic regression and multivariate Cox proportional hazards models were fit to the data, including all covariates and combining the results of the analyses of imputations. All analyses were stratified by trial. The statistical significance of odds ratio and hazard ratio (HR) estimates was evaluated according to the likelihood ratio test. All variables clinically (odds/hazard ratio value $\leqslant$0.75 or $\geqslant$1.33) and statistically ($P \leqslant 0.10$) significantly associated with OR and OS in the multivariate analyses were used for developing the new classification criteria.

The accuracy of the new definition of *sensitive*/*resistant* patients was investigated in the derivation and validation sets. The log-hazard ratios obtained from the multivariate Cox model were used to derive a prognostic score. Coefficients estimates were normalised dividing