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A prognostic index for progression-free survival in malignant mesothelioma with application to the design of phase II trials: A combined analysis of 10 EORTC trials

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ABSTRACT

Purpose: For cytostatic agents or when the response assessment is difficult, adaptations to phase II designs may allow a better assessment of therapeutic activity: first by using the progression-free survival rate (PFSR) as primary end-point instead of the response rate, and second by considering progression-free survival (PFS) risk groups based on a prognostic index (PI). In mesothelioma, current treatments yield disappointingly poor results and there is a need to investigate new regimens. The purpose of this report is to provide a PI for PFS in mesothelioma and reference values for the PFSR.

Materials and methods: Data on 523 patients included in 10 European Organisation for Research and Treatment of Cancer (EORTC) mesothelioma studies were analysed to identify prognostic factors using a multivariate Cox regression model. Subsequently, a PI and a nomogram for PFS were developed. The PFSRs at 3, 4, 5 and 6 months were estimated.

Results: A performance status > 0, stage IV disease and mixed or sarcomatous histological type were indicators of a poor prognosis for PFS. From the PI, based on these three variables, four risk groups were defined. The median progression-free survival ranged from 5.3 to 2.1 months in these risk categories. The PFSRs at 3 months were 70.6%, 62.4%, 54.2% and 42.1% in the four categories, respectively.

Conclusion: The PI allows dividing patients into homogeneous risk categories in which PFSRs can be calculated and used to design future phase II mesothelioma trials. Defining homogeneous categories of patients avoids dilution of results between groups and improves the assessment of therapeutic activity.

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1. Introduction

Malignant mesothelioma is a difficult disease to treat. Most patients with mesothelioma are not candidates for surgery or radiotherapy and chemotherapy is the only option. Historically, no agent has consistently yielded response rates over 20%. Recently, two phase III trials testing cisplatin in combination with another agent, raltitrexed[1] and pemetrexed,[2] respectively, have shown promising results when compared to those with cisplatin alone. However, the median survival remains low, between 6 and 18 months. The incidence of mesothelioma is increasing all over the world and this is not expected to stop in the next decade.[3] The development of new, more active drugs is thus needed.

Drugs inhibiting the vascular endothelial growth factor and its receptor, the epidermal growth factor receptor and the platelet-derived growth factor receptor are being tested in clinical trials in mesothelioma patients.[4] Novel targeted agents should be investigated further to determine their potential activity. Most of these agents, called cytostatic agents, stop or slow the growth of tumour. This biological antitumour activity should be taken into account in the design of phase II cancer clinical trials. Phase II trial designs have originally been developed for the investigation of cytotoxic drugs whose activity is characterised by the shrinkage of target lesions. The classical end-point is the response rate based on a decrease in tumour size. For cytostatic agents, a better approach of screening their biological antitumour activity would be to assess their impact on the progression-free survival rate (PFSR) at a fixed time point instead of the response rate.[5] Using PFSR at a fixed time point as primary end-point in phase II trials is of interest in assessing new drug activity in mesothelioma. A first paper provided reference values for PFSR which could be used to design a future phase II mesothelioma trial.[6]

One way to improve the design of new phase II trials is to take into account prognostic factors. It allows one to better assess therapeutic activity by avoiding a dilution of results between high- and low-risk patients. Moreover, clinical trials based on homogeneous risk groups allow a better comparison between trials. Several studies have reported prognostic factors for survival[7–13] in mesothelioma but not for progression-free survival (PFS). The purpose of this report is to identify prognostic factors for PFS by analysing the data of mesothelioma patients from 10 European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group trials in order to build a prognostic index (PI). This PI can be used to divide patients into groups with similar prognoses. Defining more homogeneous groups of patients may improve the design of future mesothelioma phase II trials with PFSR as primary end-point.

2. Materials and methods

Between October 1984 and January 2003, 10 mesothelioma trials (nine phase II trials and one phase III trial) were carried out by the EORTC Lung Cancer Group, and 598 patients were registered.[1,14–21]

In all these trials, a histologically or cytologically proven diagnosis of malignant mesothelioma was required. All stages of disease were eligible. Patients were chemotherapy naïve. No prior radiotherapy was allowed except palliative radiotherapy and prior surgery was permitted only if there was evidence of recurrence of disease thereafter. The presence of symptoms of central nervous system metastases was an exclusion criterion. Patients were aged from 18 to 80 years and had a World Health Organisation (WHO) performance status $\leqslant 2$. Haematological and liver function inclusion criteria for all trials were: WBC count $\geqslant 3.5$ or 4×10^9/l, platelet count $\geqslant 100 \times 10^9$/l and bilirubin level $\leqslant 25$ μmol/l. Response to therapy was evaluated according to the WHO criteria[22] in all trials except the two most recent trials[1,15] which used the RECIST criteria.[23] In all trials, patients were followed for progression and for survival. Duration of PFS and overall survival were calculated from the date of starting of the treatment to the date of progression or death from all causes.

The following factors were studied: age (years), sex, disease stage (IMIG staging system), WHO performance status, alkaline phosphatase level, lactate dehydrogenase (LDH) level, WBC count (10^9/l), platelet count (10^9/l), haemoglobin level (g/dl), histological type, certainty of histological diagnosis and the time interval from first histological diagnosis to the date of starting of the treatment. Alkaline phosphatase and LDH levels were considered as normal or abnormal according to the normal level range of each participating institution. In the three oldest trials, Butchart's staging system was used to define the stage of disease. It was converted to the IMIG staging system according to: Butchart I = IMIG stages I and II, Butchart II = IMIG any T3 or N2, Butchart III = IMIG any T4 or N3, Butchart IV = IMIG any M1. For most continuous variables, an increase in risk was not linked linearly to an increase in the value of the variable. Continuous variables were categorised to a variable on 2 or 3 levels. Cut-off points were chosen from the literature for age and haemoglobin, and tertiles were used for other variables.

PFS and survival were estimated using the Kaplan–Meier method. The Cox proportional hazards model stratified by clinical trial was used for both univariate and multivariate analyses. The proportional hazards assumption held for each variable under study. The multivariate Cox regression was developed including all variables used in the univariate analysis. Firstly, a backward selection procedure was used based on Akaike's corrected information criterion. Secondly, the benefit of each variable selected in the multivariate regression was assessed using the following criteria: the deviance (–2 log likelihood), Akaike's information criterion, Schwartz's Bayesian information criterion and the *c* (concordance) index. The first three criteria characterise the quality of the fitted model. The *c* index measures the discrimination power of the model. A *c* index = 1 indicates a perfect separation of patients according to the outcomes and *c* index = 0.50 indicates chance agreement. Calibration curves showing the agreement between observed and predicted outcomes over a range of predicted probabilities were also drawn. The bias adjusted *c* index and the calibration curves were calculated by bootstrapping 200 samples with replacement from the original patients used to fit the Cox model.[24] Based on these different criteria, a final multivariate regression was selected. From this multivariate regression, a prognostic index for PFS (PI_p) and a nomogram[25] predicting PFS probabilities at 3, 4, 5 and 6 months were

developed. The PFSRs at 3, 4, 5 and 6 months in different risk categories were estimated by the Kaplan–Meier method.

Afterwards, a multivariate regression for survival was built with the variables selected in the PFS regression. Subsequently, a prognostic index (PI_s) and a nomogram for survival were also developed.

Analyses were performed using SAS 9.1 and R 2.5.1 statistical software.

3. Results

From the 598 patients registered, 75 were excluded (for ineligibility ($n = 41$), for incoherent or missing data ($n = 9$), histological diagnosis not definite or probable ($n = 25$)). The remaining 523 patients were predominantly male (83%) with a performance status of 0 or 1 (86%). The median age was 58 years (range: 19–80 years). Mesothelioma diagnosis was definite in 89% and probable in 11%. Histological type was epithelial in 69%, sarcomatous in 8% and mixed in 23%. Forty-one percent of patients had a stage III disease and 33% had a stage IV disease. The median WBC count, platelet count and haemoglobin concentration were 8.4×10^9/l (range: 3.2–18.3×10^9/l), 374×10^9/l (range: 153–968×10^9/l) and 13.2 g/dl (range: 6.4–19.6 g/dl), respectively. LDH level was abnormal in 18% (58/322) and alkaline phosphatase level was abnormal in 31% (109/355).

Median follow-up time was 9.9 months (IQR: 4.5–22.8 months). Of the 523 patients, 485 (93%) progressed during follow-up and 445 (85%) died, leading to 3% (18/523) of progression-free survivors after the follow-up. Median survival and median PFS were 9.1 months (95% confidence interval (CI): 8.3–10.2 months) and 3.9 months (95% CI: 3.4–4.3 months), respectively.

In univariate analysis of PFS (Table 1), poor prognosis was associated with age < 60 years, high WBC count ($\geqslant 7.4 \times 10^9$/l), haemoglobin concentration < 12 g/dl, performance status greater than 0 and an abnormal LDH level. A moderate increase in platelet count was associated with an increased risk but without reaching statistical significance; a high level was clearly significantly associated with an increased risk. Stage IV disease was associated with a poor prognosis compared with stage I and II disease. A better prognosis was associated with epithelial histological type as compared with mixed or sarcomatous type. Time interval since diagnosis ($p = 0.450$), gender ($p = 0.875$), alkaline phosphatase level ($p = 0.121$) and certainty of histological diagnosis ($p = 0.343$) did not reach significance for predicting PFS. For the variables of histological type, stage of disease and WBC count, different categories had similar HRs, and thus they were regrouped before their inclusion in the multivariate analysis.

After a multivariate backward selection procedure, the following prognostic factors were retained: histological type, stage of disease, performance status, WBC count, age, haemoglobin concentration, and certainty of histological diagnosis. The latter was not significant in the univariate analysis but it was retained in the multivariate regression due to its interaction with the WBC count ($\chi^2 = 7.65$, $p = 0.022$). Consequently, the interaction between these two clinical factors was included in the multivariate regression. Table 1 shows the results of the multivariate regression with these seven covariates. The statistical criteria (–2 log likelihood, Akaike's information criterion and Schwartz's Bayesian information criterion) showed that haemoglobin, age, WBC count and certainty of histological diagnosis did not have an important benefit. After removing these covariates from the regression, the *c* index decreased slightly from 0.601 to 0.582. The calibration curves (Fig. 1) supported the lack of improvement in including these four variables. Because of the parsimony principle, the regression including performance status, disease stage and histological type was selected as the final multivariate regression. A performance status greater than 0, stage IV disease and mixed or sarcomatous type were associated with a poor prognosis. The influence of these three clinical factors was also relevant on survival (Table 2).

Prognostic indices (PI_p for PFS and PI_s for survival) were computed as the sum of points attributed to each level of these three covariates. These points were calculated by rescaling the model-derived beta coefficients to a scale that goes from 0 to 100 points.[25] For PFS, epithelial type corresponded to 42 points, stage IV corresponded to 37 points and performance status of 1/2 corresponded to 50/100 points. For survival, these points were 44, 38 and 50/100 points, respectively. According to the patient's individual characteristics for these three covariates, PI_p values ranged from 0 to 179 and PI_s values ranged from 0 to 182. Nomograms for predicting PFS and survival probabilities at 3, 4, 5 and 6 months are shown in Fig. 2. For instance, a patient with non-epithelial, stage IV disease and a performance status of 1 has PI_p of 129 points and PI_s of 132 points. From the nomogram, this patient's probability of remaining free from cancer progression or death at 3 months is 0.32 and his survival probability at this time is 0.70.

In order to show the interest of these PIs, we defined four risk categories: patients with PI = 0 (e.g. epithelial type, no stage IV and performance status = 0), patients with $0 < PI \leqslant 60$ (e.g. either no epithelial or stage IV or performance status = 1), patients with $60 < PI \leqslant 120$ (e.g. two of the latter or performance status = 2) and patients with PI > 120. Regardless of the prognostic index used (PI_p or PI_s), patients were divided into the same four risk categories. Fig. 3 illustrates the PFS and survival for each risk category. The median PFS for patients with $PI_p = 0$ was 5.3 (95% CI: 3.4–7.6) months and 2.1 (95% CI: 1.7–3.5) months for patients with $PI_p > 120$. The median PFS in the two intermediate risk categories was not significantly different: 4.1 (95% CI: 3.4–6.1) and 3.6 (95% CI: 2.6–4.7) months, respectively. The survival for the four risk categories was 15.6 (95% CI: 12.0–18.4), 10.9 (95% CI: 9.2–13.4), 8.0 (95% CI: 6.6–8.9) and 5.4 (95% CI: 4.6–6.5) months, respectively.

The PFSRs at 3, 4, 5 and 6 months in the each risk category are shown in Table 3.

4. Discussion

The literature does not report previous studies on prognostic factors for PFS, but reports only for survival. Prognostic scoring systems for survival have been proposed by the EORTC[8] and by the Cancer and Leukaemia Group B (CALGB).[10] The EORTC's survival scoring index included: white blood cell

Table 1 – Prognostic value of clinical factors for progression-free survival.

Clinical factors	N	Progression or death, n	Univariate			Multivariate		
			HR	[95% CI]	p-Value	HR	[95% CI]	p-Value
Age (years)					**0.040**			**0.045**
⩾60	232	219	1			1		
<60	291	286	**1.21**	**[1.01–1.46]**		**1.26**	**[1.01–1.58]**	
Histological type					**0.007**			**0.004**
Epithelial	310	299	1			1		
Mixed	102	99	**1.39**	**[1.09–1.77]**	]	**1.43**	**[1.12–1.82]**	
Sarcomatous	38	36	**1.44**	**[1.01–2.06]**				
Stage of disease					**0.027**			**0.044**
Stage I or II	118	112	1		]	1		
Stage III	190	184	1.06	[0.83–1.35]				
Stage IV	154	151	**1.37**	**[1.05–1.8]**		**1.28**	**[1.01–1.62]**	
Performance status					**<0.001**			**0.001**
0	136	128	1			1		
1	313	305	**1.44**	**[1.24–1.68]**		**1.36**	**[1.13–1.63]**	
2	74	72	**2.08**	**(Log linear trend)**		**1.84**	**(Log linear trend)**	
Haemoglobin concentration					**<0.001**			**0.044**
⩾12 g/dl	379	364	1			1		
<12 g/dl	141	139	**1.47**	**[1.2–1.81]**		**1.29**	**[1.01–1.64]**	
Histological diagnosis					0.343			
Probable	54	52	1					
Definite	447	431	1.16	[0.86–1.56]				
WBC count (10^9/l)					**0.006**			
–, 7.4[	166	159	1					
[7.4–9.5[	180	174	**1.37**	**[1.09–1.71]**				
[9.5, –	175	170	**1.38**	**[1.1–1.72]**				
Interaction: histological diagnosis × WBC count								**0.031**
When histological diagnosis is probable and WBC count is	NA							
$<7.4 \times 10^9$/l						1		
$\geqslant 7.4 \times 10^9$/l						0.48	[0.19–1.22]	
When histological diagnosis is definite and WBC count is	NA							
$<7.4 \times 10^9$/l						1		
$\geqslant 7.4 \times 10^9$/l						**1.39**	**[1.09–1.78]**	
Platelets count (10^9/l)					**0.041**			
–, 315[	173	162	1					
[315–435[	172	169	1.22	[0.97–1.52]				
[435, –	176	172	**1.33**	**[1.06–1.67]**				0.451
LDH level					**0.002**			
Normal	264	254	1					
Abnormal	58	58	**1.64**	**[1.22–2.21]**				0.604

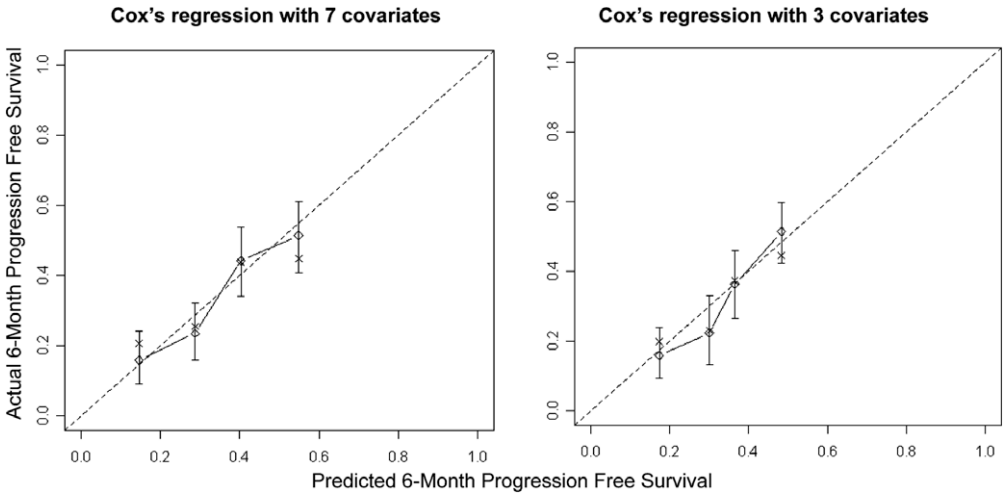

Fig. 1 – Calibration curves for 6-month progression-free survival. The dashed line indicates ideal reference line where predicted probabilities would match the observed outcome. The solid line represents the performance of current model. ◇ = subgroup estimates, x = bootstrap-corrected estimate of model performance and vertical bars = 95% CI.

Table 2 – Multivariate Cox's regressions with three prognostic factors for progression-free survival and for survival[a].

Covariates	N	Progression or death				Death			
		n	HR	[95% CI]	*p*-Value	*n*	HR	[95% CI]	*p*-Value
Histological type					0.012				0.0002
Epithelial	266	257	1			224	1		
Mixed or sarcomatous	114	111	1.35	[1.07–1.72]		103	1.60	[1.2–1.71]	
Stage of disease					0.026				0.0014
Stage I or II or III	247	238	1			208	1		
Stage IV	133	130	1.31	[1.03–1.65]		119	1.49	[1.17–1.91]	
Performance status (WHO scale)					<0.0001				<0.0001
0	97	90	1			71	1		
1	233	229	1.43	[1.2–1.71]		208	1.70	[1.4–2.06]	
2	50	49	2.04	(Log linear trend)		48	2.89	(Log linear trend)	

Regression performed on 380 patients for which three prognostic factors were known.

count > 8.3×10^9/l, performance status $\geqslant 1$, sarcomatoid tumour cell type, probable or possible histological diagnosis and male gender. The high-risk group was defined as having at least three or more of these factors. The CALGB index is more complex and combined six prognostic factors (performance status, age, haemoglobin, white blood cell, presence of chest pain and weight loss) in order to characterise six prognostic groups.

In the case of malignant mesothelioma, the results for PFS should not be very different from those observed for survival. Indeed, malignant mesothelioma is an aggressive and nearly always fatal disease.[12] In our study, 93% (485/523) of patients progressed and 88% (425/485) died over the follow-up period. Except for gender, all variables in the EORTC's scoring index were significant for PFS in our results. This was expected because this index was based on the data coming from five trials which are part of the 10 trials included in our study. All variables of the CALGB index were significant in our results for PFS except for the presence of chest pain and weight loss which were not measured in our studies.

Our PI for PFS included three variables: performance status, histological subtype and stage of disease. Performance status and histological subtype were found to be significant in all studies for survival. The impact of the stage on survival remains controversial.[9] This could be explained by the inadequacy of staging in the case of mesothelioma. Indeed, surgical tumour staging is not routinely done and radiological staging only has a limited predictive value and seems poorly reproducible.[7] However, the extent of disease and lymph node involvement have been shown to be related to survival.[26] Table 2 shows a relevant impact of the three prognostic factors selected for PFS on survival supporting their prognostic value.

Our PI_p allows the definition of risk categories for PFS which should be considered when designing future phase II mesothelioma trials with PFSR as primary end-point. Indeed, it is important to adapt to the design of a phase II trial according to the treatment and the disease. On one hand, the PFSR at a fixed time point is a better end-point than the classical response rate in assessing the new targeted therapies.[5,6,27] On another hand, taking into account a homogeneous risk group

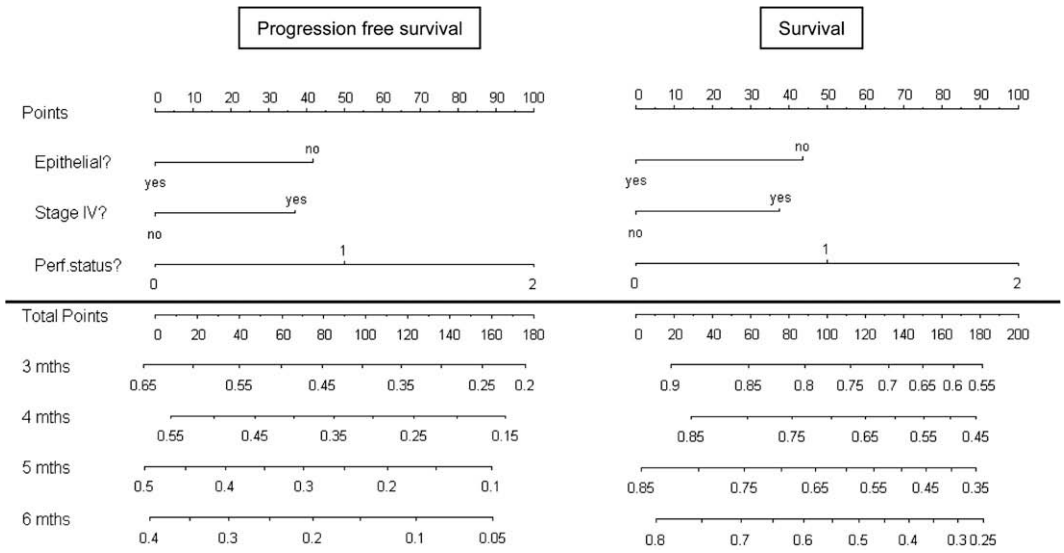

Fig. 2 – Nomograms for progression-free survival and for survival. A nomogram is used as follows: (1) locate a patient on each prognostic factor scale, (2) sum the points to define total points, (3) draw a vertical line from the total points axis straight down to the patient's probability axes of PFS (left) or survival (right) for 3, 4, 5 and 6 months.

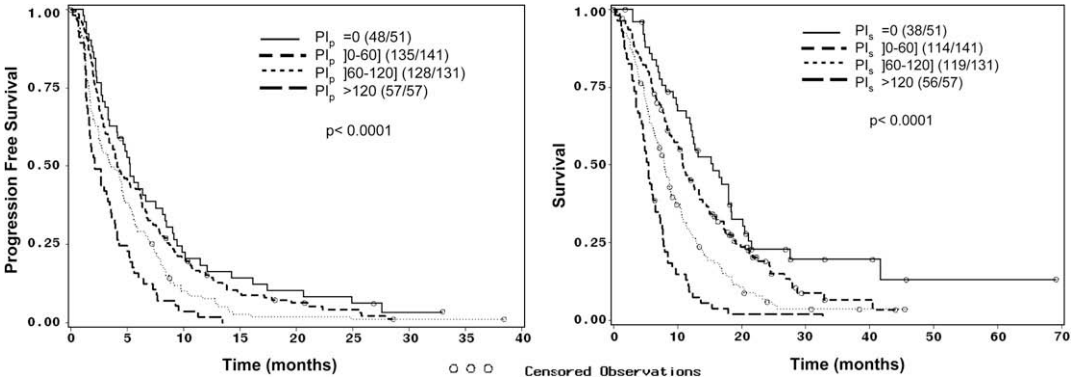

Fig. 3 – Progression-free survival and survival curves for different risk categories based on the prognostic index value: PI_p for PFS and PI_s for survival.

Table 3 – Progression-free survival rates at 3, 4, 5 and 6 months (%).

	At 3 months [95% CI]	At 4 months [95% CI]	At 5 months [95% CI]	At 6 months [95% CI]
$PI_p = 0$	71% (56–81)	63% (48–74)	53% (38–65)	45% (31–58)
$0 < PI_p \leqslant 60$	62% (54–70)	55% (46–62)	45% (37–53)	43% (34–51)
$60 < PI_p \leqslant 120$	54% (45–62)	49% (40–57)	38% (30–46)	29% (22–37)
$PI_p > 120$	42% (29–54)	32% (20–44)	23% (13–34)	16% (8–26)

PI = prognostic index.

for PFS may increase the accuracy of assessing therapeutic activity. To design a future phase II mesothelioma trial, two success rates should be determined: P0 and P1 which correspond to insufficient activity and sufficient activity limits, respectively. Using PFSR as primary end-point, the success rates are PFSR at a fixed time point. Table 3 reports the PFSRs

at 3, 4, 5 and 6 months for each risk category and can be used as reference values to determine P0 and P1. The definition of these four risk categories is an illustration. Other risk categories could be defined from the PI_p and afterwards the PFSR could be calculated in each category. For instance, the PFSRs at 3 and 6 months for patients with $PI_p \leqslant 60$ and for patients with $PI_p > 60$ were 64.6% (95% CI: 57.4–70.9) and 50.5% (95% CI: 43.2–57.4), respectively. Thus, in order to design a future phase II mesothelioma trial, P0 should be defined between 57% and 71% in the low-risk group and in the high-risk group between 43% and 57%.

Our PI_p could also be considered in the design of phase III trials with PFS as the main end-point.

In our work, there were nine phase II trials and one phase III trial that accounted for approximately 50% of data and which were carried out consecutively. All trials were organised by the EORTC according to similar protocols. The eligibility criteria were similar among the trials. This supports a homogeneous data pool. However, the distribution of all studied clinical variables in the different trials was not completely comparable. But our PI discriminated risk groups in the pool of all phase II trials data ($p = 0.0002$) and in the phase III trial data ($p = 0.0005$). This supports the validity of our results.

A $c = 0.582$ for our multivariate regression indicated a not very high discrimination power of the estimated equation that needs to be validated on an external independent data set. However, we are bringing relevant and not yet published data about prognostic factors of progression-free survival in mesothelioma. Our work highlights that the development of a prognostic index for PFS is relevant and deserves more investigations.

In the future, biological markers or quality of life indicators may provide additional information on mesothelioma and will help in prognostication.[11,28] For example, Bottomley et al. have shown that pain and appetite loss might be independent prognostic factors for survival in patients with advanced malignant mesothelioma.[29]

In conclusion, in the case of mesothelioma the results of current treatments are poor and thus the development of new more active regimens, including particularly the targeted therapies, is urgently required. Therefore, adjustments in the design of phase II trials could allow a better assessment of therapeutic activity of these new treatments: firstly by using the PFSR as primary end-point instead of the classical response rate, and secondly by considering different risk groups of PFS based on a prognostic index. First has already been used in practice. Indeed, the EORTC Lung Cancer Group is currently carrying out a phase II trial of Bortezomib with cisplatin as first line treatment of malignant mesothelioma using the progression-free survival rate at 18 weeks as the primary end-point (ClinicalTrials.gov, Nr. NCT00458913). Our prognostic index for PFS could be considered at either the design stage or the analysis stage when interpreting the results.

Conflict of interest statement

None declared.

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