Health-Related Quality of Life Impact from Adding Bevacizumab to Cisplatin-Pemetrexed in Malignant Pleural Mesothelioma in the MAPS IFCT-GFPC-0701 Phase III Trial

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Abstract

**Purpose:** The IFCT-GFPC-0701 MAPS phase III trial highlighted significant improvement in overall survival from adding bevacizumab to the standard first-line chemotherapy regimen [cisplatin plus pemetrexed (PC)] in advanced malignant pleural mesothelioma (MPM). We present the results of health-related quality of life (HRQoL), a secondary endpoint of MAPS.

**Patients and Methods:** HRQoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and the lung cancer-specific module QLQ-LC13 at randomization and then every 9 weeks until disease progression. HRQoL deterioration–free survival (QFS), used to analyze longitudinal HRQoL data, was defined as the interval between randomization and the occurrence of the first clinically relevant definitive deterioration compared with the HRQoL score at baseline, or death.

**Results:** A total of 448 patients were included in the MAPS trial between 2008 and 2014. At baseline, 425 patients (94.8%) completed the HRQoL questionnaire. We report that adding bevacizumab to cisplatin and pemetrexed (PCB) significantly improved QFS for the peripheral neuropathy dimension, with a median QFS of 12.09 months [95% confidence interval (CI), 9.59–13.67] in the PCB arm versus 7.59 months (95% CI, 6.57–8.61) in the PC arm [HR (PCB vs. PC) = 0.74; 95% CI, 0.61–0.91; P = 0.004]. QFS was also longer in the PCB arm for the pain dimension (HR = 0.84; 95% CI, 0.69–1.02; P = 0.08).

**Conclusions:** This study demonstrated that adding bevacizumab to standard chemotherapy in patients with advanced MPM had no negative impact on HRQoL. A significant improvement in the peripheral neuropathy and pain HRQoL dimensions was even observed.

Introduction

Pleural mesothelioma causes over 43,000 deaths worldwide each year (1). Malignant pleural mesothelioma (MPM) is primarily associated with occupational exposure to asbestos. The incidence of MPM could potentially continue to grow in the future (2).

Vascular endothelial growth factor (VEGF) is one of the most relevant endothelial angiogenic factors, expressed by virtually all Cooperative Thoracic Group (IFCT), Paris, France. 25Department of Thoracic Oncology, Centre d’investigation clinique Institut national de la santé et de la recherche médicale I25, Hospital Bichat-Claude Bernard, Assistance Publique-Hôpitaux de Paris, Paris-Diderot University (Paris 7), Paris, France. 26Department of Pulmonology and Thoracic Oncology, University of Caen, Centre Hospitalier Universitaire Côte de nacre, Caen, France.

**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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In the international, randomized, multicenter, phase III trial (IFCT-GFPC-0701 MAPS) in advanced malignant pleural mesothelioma (MPM), the increase in bevacizumab-related toxicities did not translate to health-related quality of life (HRQoL) deterioration. Moreover, longitudinal analysis of HRQoL showed that the addition of bevacizumab to cisplatin and pemetrexed significantly improved one HRQoL dimension, namely peripheral neuropathy, and showed a trend toward improvement in the pain dimension.

These data may help the practice evolve by providing interest in the addition of bevacizumab to the standard first-line chemotherapy regimen (cisplatin plus pemetrexed) in MPM.

Most clinical trials now integrate HRQoL as one of the major endpoints to investigate the clinical benefit of therapy for the patient. The deterioration-free survival method we applied for the longitudinal HRQoL analysis might be reported more systematically in other clinical trials.

Health-related quality of life

HRQoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (8) and the lung cancer–specific module QLQ-LC13 (9) questionnaire, validated in patients treated with chemotherapy in mesothelioma (10). Both were completed at randomization and then every 9 weeks until disease progression. Paper questionnaires were given to the patients and filled in, by the patients themselves, at the hospital, before consultation with the oncologist.

The QLQ-C30 is a 30-item cancer-specific tool (11), enabling assessment of 5 functional scales (physical, role, cognitive, social, and emotional), a global QoL scale, and nine symptom scales (nausea and vomiting, pain, fatigue, dyspnea, sleeping disturbances, appetite loss, constipation, diarrhea, and financial difficulties; ref. 8).

The QLQ-LC13 was developed and validated specifically for patients with lung cancer (9). It includes 13 items that address lung cancer symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related adverse effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and pain medication.

We computed the HRQoL scores using the EORTC Scoring Manual and standardized them on a 0 to 100 scale. A high score reflected a high functional level, high global quality of life level, and high symptomatic level (12).

Statistical analysis

The primary objective of MAPS was to demonstrate if significant improvement in OS was achieved by adding bevacizumab to standard first-line chemotherapy (cisplatin plus pemetrexed; ref. 5) in advanced MPM. HRQoL was a secondary endpoint of the trial. This was analyzed on the modified intent-to-treat (mITT) population, defined as all intent-to-treat patients for whom at least one baseline HRQoL score was available.

The analysis was conducted according to the patient-reported outcome Consolidated Standards of Reporting Trials (CONSORT) statement (13). Each dimension of the QLQ-C30 and QLQ-LC13 was studied. Baseline characteristics including HRQoL scores of the patients were described by treatment arms in the mITT population. Qualitative variables were described using frequencies and percentages and compared using a Chi-square or a Fisher exact test. Quantitative variables were described using mean and SD and compared using a T test or a nonparametric Mann–Whitney test.

HRQoL deterioration-free survival (QFS) was used as the modality of longitudinal analysis. It was defined as the interval between randomization and the occurrence of the first deterioration representing a minimal clinically important difference (MCID) of 5 points (14) compared with the HRQoL score at baseline, with no further improvement in HRQoL score ≥ 5 points as compared with baseline score, or death (15). Patients still alive at the last follow-up were censored if no significant
definitive deteriorations in their HRQoL score were observed before. Patients with baseline scores but no follow-up score were censored immediately after baseline (Day 1). Only questionnaires completed at the planned measurement times according to protocol were included in the analysis. Thus, in case questionnaires had been completed on the visit at which progression was determined or after, they were excluded from the analysis.

The QFS curves were calculated using the Kaplan–Meier estimation method, described using medians with 95% CIs, and compared between treatment arms using log-rank tests. The univariate Cox model was applied to estimate HRs with their 95% CIs. We assessed the impact of following baseline variables in univariate analysis: treatment arm, age, gender, performance status, smoking status, weight loss, hemoglobin level, and histology. All variables with a univariate P-value <0.1 were eligible for a multivariate Cox regression model in order to identify factors independently associated with QFS. The variables for multivariate analysis were selected with consideration of colinearity between variables. The treatment arm variable was forced into the multivariate model.

In case of a missing questionnaire between 2 available measurement times, the last HRQoL scores obtained before the missing evaluation were used. It means that HRQoL level remains constant between 2 available assessment times. For missing items, according to recommendations of the EORTC scoring manual for calculating the scale scores, if at least half of the items from the scale had been answered, missing items were given values equal to the average of the present items (12). If there were not half of the items, the score was considered as missing. For single-item measures, the score was considered as missing. Compliance to HRQoL questionnaires was assessed by treatment arms, for each measurement time. In case of a difference in compliance between treatment arms, a comparison between completers and non-completers was made according to baseline characteristics, PFS, and OS of noncompleters.

A P-value of 0.05 or lower was considered statistically significant. No adjustment for multiple testing was made since HRQoL was a secondary endpoint. All analyses were performed using SAS software, Version 9.3 (SAS Institute), and R software (Version 3.4) using the QoLR package (16).

Results

Patients and HRQoL scores at baseline

A total of 448 patients with advanced MPM were included in the IFCT-GFPC-0701 MAPS study between February 2008 and January 2014. At baseline, 217 of 225 patients (96.4%) in the PC group had at least 1 HRQoL score available, versus 208 of 223 (93.3%) in the PCB group (Fig. 1). The baseline characteristics of these patients were well balanced. They comprised 324 males (76.2%), the mean age was 65.1 years (SD = 7), 410 exhibited performance status 0 to 1 (96.5%), 180 nonsmokers (42.4%), the mean weight loss was 3.6% (SD = 4), and 346 patients (81.4%) had epithelioid mesothelioma. The baseline HRQoL scores did not differ between arms. The mean score for global health status at baseline was 59 (SD = 20.1) and 60 (21.4), respectively (P = 0.52; Table 1).

Compliance with HRQoL questionnaires during follow-up

Compliance to HRQoL questionnaires over time is presented in Fig. 1. The total numbers of questionnaires completed with at least 1 HRQoL score available were: 146 in 255 patients (57.25%) at 27 weeks, and 37 in 71 patients (52.11%) at 54 weeks. From week 27, compliance was higher in the PC arm. The difference was statistically significant at weeks 27 (P-value Chi-square 0.003), 36

Figure 1. Flow chart for HRQoL data.
Table 1. HRQoL scores at baseline according to treatment arm

<table>
<thead>
<tr>
<th>Scores</th>
<th>PC (N = 217)</th>
<th>PCB (N = 208)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>Median (min-max)</td>
</tr>
<tr>
<td>QLQ-C30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global health status</td>
<td>215</td>
<td>59.0 (20.3)</td>
<td>58.3 (0-100)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>216</td>
<td>78.2 (20.6)</td>
<td>86.7 (13.3-100)</td>
</tr>
<tr>
<td>Role functioning</td>
<td>215</td>
<td>66.5 (19.9)</td>
<td>66.7 (0-100)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>216</td>
<td>69.4 (22.5)</td>
<td>75.0 (8.3-100)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>216</td>
<td>89.0 (16.2)</td>
<td>100 (86.7-100)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>216</td>
<td>75.4 (29.8)</td>
<td>83.3 (0-100)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>215</td>
<td>36.1 (26.2)</td>
<td>33.3 (0-100)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>216</td>
<td>4.6 (12.2)</td>
<td>0 (0-66.7)</td>
</tr>
<tr>
<td>Pain</td>
<td>216</td>
<td>29.0 (28.2)</td>
<td>33.3 (0-100)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>216</td>
<td>35.2 (31.1)</td>
<td>33.3 (0-100)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>215</td>
<td>31.8 (32.8)</td>
<td>33.3 (0-100)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>215</td>
<td>22.8 (30.8)</td>
<td>0 (0-100)</td>
</tr>
<tr>
<td>Constipation</td>
<td>215</td>
<td>19.7 (29.9)</td>
<td>0 (0-100)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>214</td>
<td>4.8 (14.2)</td>
<td>0 (0-100)</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>213</td>
<td>5.5 (15.1)</td>
<td>0 (0-100)</td>
</tr>
<tr>
<td>QLQ-LC13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>206</td>
<td>26.0 (21.3)</td>
<td>22.2 (0-100)</td>
</tr>
<tr>
<td>Coughing</td>
<td>202</td>
<td>25.6 (23.3)</td>
<td>33.3 (0-100)</td>
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<tr>
<td>Hemoptysis</td>
<td>205</td>
<td>0.0 (0)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Sore mouth</td>
<td>204</td>
<td>1.8 (8.2)</td>
<td>0 (0-66.7)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>206</td>
<td>2.9 (11.0)</td>
<td>0 (0-66.7)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>205</td>
<td>1.8 (9.5)</td>
<td>0 (0-100)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>206</td>
<td>1.3 (7.2)</td>
<td>0 (0-100)</td>
</tr>
<tr>
<td>Pain in chest</td>
<td>205</td>
<td>24.1 (27.5)</td>
<td>33.3 (0-100)</td>
</tr>
<tr>
<td>Pain in arm or shoulder</td>
<td>203</td>
<td>15.8 (26.2)</td>
<td>0 (0-100)</td>
</tr>
<tr>
<td>Pain in other parts</td>
<td>190</td>
<td>14.4 (22.3)</td>
<td>0 (0-66.7)</td>
</tr>
</tbody>
</table>

Abbreviations: PCB, pemetrexed plus cisplatin plus bevacizumab; PC, pemetrexed plus cisplatin. P value, Mann-Whitney nonparametric test; QLQ-C30, quality of life (cancer-specific) questionnaire; QLQ-LC13, quality of life (lung cancer-specific) questionnaire.

Discussion

Our analysis of the phase III IFCT-GFPC-0701 MAPS trial revealed that the increase in bevacizumab-related toxicities did not translate to HRQoL deterioration. Moreover, longitudinal analysis of HRQoL showed that the addition of bevacizumab to cisplatin and pemetrexed significantly improved QFS with a MCID of 5 points for 1 HRQoL dimension, peripheral neuropathy, with a clinically meaningful increase of 4 months in the median QFS (HR = 0.74; 95% CI, 0.61–0.91; P = 0.004), and a trend towards improved QFS for the pain dimension.

In a phase II trial of 53 patients treated with cisplatin–gemcitabine for MPM, HRQoL was evaluated using the same questionnaires as in our study. This study supported the validity of the EORTC QLQ-C30 and QLQ-LC13 questionnaires as outcomes for MPM. Pain and coughing were significantly improved with chemotherapy (10). There are no guidelines currently recommending the use of a specific questionnaire for HRQoL studies for patients with MPM. The most frequently used questionnaires in the literature include the EORTC QLQ-C30 and QLQ-LC13, the Lung Cancer Symptom Scale (LCSS)-meso and the FACT-L questionnaires (17). The EORTC QLQ-C30 and the QLQ-LC13 questionnaires have been specifically validated in patients with MPM treated with chemotherapy by Nowak and colleagues (10). The LCSS-meso includes the same items as the LCSS except for the deletion of one item, hemoptysis, and was published in 2004 (18). A drawback of the LCSS is that it ignores components of HRQoL, such as the social and emotional aspects (19). The comparison between LCSS and other HRQoL instruments demonstrated a reasonably good reliability and validity for the other components. Actually, the LCSS-meso was also completed by patients in this study, but did not add any information (data not shown). The acceptability of the FACT-L questionnaire,
although frequently used, has been compared with the EORTC questionnaire in patients with MPM and was shown to be significantly lower (20).

In a Phase III trial of cisplatin with or without raltitrexed in 250 patients with MPM, HRQoL analysis using the same questionnaires showed an improvement in dyspnea over time (21). In a series of 63 consecutive patients, including 58 patients treated with first-line platinum-pemetrexed and 15 patients who opted for best supportive care, analysis of HRQoL using the EORTC QLQ-C30 and QLQ-LC13 questionnaires revealed deterioration in global HRQoL, dyspnea, and pain in the best supportive care group (22). The trend observed in our study with a nonsignificant improvement of 2 months in the median QFS for pain or death in the PCB arm may indicate further improvement of a key symptom with the addition of bevacizumab, and is understandable given the context of improved response and progression-free survival in the PCB arm (5). The relationship between peripheral neuropathy and bevacizumab is, however, puzzling, with increased median QFS over 4 months observed for peripheral neuropathy in the PCB arm. There was no difference between the groups in terms of physician-reported frequency and peripheral neuropathy severity (5). In non–small cell lung cancer, adding bevacizumab to carboplatin-paclitaxel, a more neurotoxic chemotherapy regimen compared with cisplatin-pemetrexed, did not influence the risk of peripheral neuropathy (4). Bevacizumab has been occasionally reported to improve neuropathy symptoms in polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome (23). Recently, bevacizumab was proven protective against experimental diabetic neuropathy by its capacity to neutralize Schwann cell-secreted VEGF, restoring neurite outgrowth (24).

An important challenge of the analysis of HRQoL that could influence our results is the multiplicity of tests performed, due to
In our trial, compliance levels were high at baseline, with around 5% missing data. The quality of our longitudinal analysis consisted of frequent HRQoL evaluations covering a long period. Long-term compliance was good, with over 50% patients answering the questionnaires at 54 weeks, which compares favorably with published compliance rates in MPM (10, 21, 22). Compliance to HRQOL questionnaires over time was better in the PC arm with a significant difference since 27 weeks. In the literature, it is generally admitted that non-compliant patients are usually the ones with deterioration in their HRQoL (26). To the best of our knowledge, imputation techniques for missing data are only exploratory and not validated or recommended yet, for longitudinal HRQoL calculations using survival analyses such as QFS. Because QFS was calculated with death considered as an event, QFS allows capturing the HRQoL deterioration of nonresponders when such patients are close to death. There was no significant difference between compliant and noncompliant patients at week 27 neither in baseline characteristics nor in PFS or OS. Although we cannot exclude that this discrepancy in compliance between both groups from week 27 could have influenced the results of our HRQoL analysis, we therefore consider that it is unlikely.

Increased cardiovascular adverse events, including low-grade hemorrhage, hypertension, and thromboembolic events reported in the PCB arm did not translate into HRQoL impairment. Except for hemoptysis, which is a rare event in pleural mesothelioma, these symptoms were not evaluated by a specific HRQoL dimension. The more general HRQoL dimensions such as overall health status, physical functioning, or fatigue are probably not sensitive enough to capture these events. Moreover, a proportion of patients who experienced these bevacizumab-induced adverse events might have been asymptomatic.

In conclusion, not only has adding bevacizumab to standard first-line chemotherapy regimen (cisplatin-pemetrexed) proven able to enhance progression-free survival and OS, it also caused no deterioration in HRQoL. The result was quite the contrary, with a trend towards improved QFS for pain and a significantly longer QFS for peripheral neuropathy; with the latter effect being potentially the consequence of an actual biological effect of bevacizumab.

**Disclosure of Potential Conflicts of Interest**

A. Anota reports receiving speakers bureau honoraria from Roche and other remuneration from Bristol-Myers Squibb and AstraZeneca. A. Scherpereel is a consultant/advisory board member for Roche, Bristol-Myers Squibb, MSD, and AstraZeneca. C. Audigier-Valette is a consultant/advisory board member for Roche and Lilly. D. Moro-Sibilot is a consultant/advisory board member for Lilly, Roche, Bristol-Myers Squibb, MSD, AstraZeneca, Boehringer, Pfizer, Takeda, and Novartis. O. Molinier is a consultant/advisory board member for Bristol-Myers Squibb, Boehringer Ingelheim, and AstraZeneca. H. Lena is a consultant/advisory board member for Lilly and Roche. V. Gounant is a consultant/advisory board member for Roche. G. Zalcman reports receiving speakers bureau honoraria from Roche and is a consultant/advisory board member for Roche and Lilly. V. Westeel reports receiving speakers bureau honoraria from Roche and Boehringer Ingelheim, and is a consultant/advisory board member for Lilly and Roche. V. Westeel also receives speakers bureau honoraria from Roche and is a consultant/advisory board member for Roche and Lilly. C. Audigier-Valette reports receiving speakers bureau honoraria from Roche and Lilly. F. Morin, D. Moro-Sibilot, O. Molinier, H. Lena, and V. Gounant report receiving speakers bureau honoraria from Roche and other remuneration from Roche and Boehringer Ingelheim. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. Eberst, A. Anota, A. Scherpereel, J. Mazieres, L. Gzellier, F. Charton, F. Morin, G. Zalcman, V. Westeel
Writing, review, and/or revision of the manuscript: G. Eberst, A. Anota, A. Scherpereel, J. Mazieres, G. Zalcman, L. Gzellier, C. Audigier-Valette, D. Moro-Sibilot, O. Molinier, H. Léna, F. Rivière, H. Janicot, F. Charton, F. Morin, G. Zalcman
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G. Eberst, D. Moro-Sibilot, F. Morin, G. Zalcman, V. Westeel
Study supervision: G. Eberst, A. Anota, A. Scherpereel, D. Moro-Sibilot, F. Morin, G. Zalcman, V. Westeel
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References


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