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Health-related quality-of-life assessment in CLEOPATRA, a phase III study combining pertuzumab with trastuzumab and docetaxel in metastatic breast cancer

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Background: The phase III CLEOPATRA study demonstrated that combining pertuzumab with trastuzumab plus docetaxel significantly improves progression-free and overall survival in previously untreated HER2-positive metastatic breast cancer. Here, we report health-related quality-of-life (HRQoL) results from CLEOPATRA.
Patients and methods: Participants were randomly assigned to pertuzumab or placebo, each given with trastuzumab plus docetaxel every 3 weeks. Pertuzumab and trastuzumab were administered until progression and six or more docetaxel cycles were recommended. Time from randomization to a ≥5-point decrease in Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) of the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire was analyzed as a prespecified secondary end point. A *post hoc* exploratory analysis investigated time to ≥2-point deterioration in Breast Cancer Subscale (BCS) score.
Results: Time to ≥5-point decline in TOI-PFB did not differ significantly between the pertuzumab and placebo arms [hazard ratio (HR), 0.97; $P = 0.7161$]. The median times to TOI-PFB deterioration were 18.4 and 18.3 weeks, respectively (approximately six cycles). The mean TOI-PFB declined slightly until week 18 and recovered thereafter. Pertuzumab increased time until BCS deterioration versus placebo (median 26.7 versus 18.3 weeks; HR, 0.77; $P = 0.0061$).
Conclusions: Combining pertuzumab with trastuzumab and docetaxel had no adverse impact on HRQoL and may prolong time to worsening of breast cancer-specific symptoms.
Key words: docetaxel, health-related quality-of-life, metastatic breast cancer, pertuzumab, trastuzumab

introduction

The human epidermal growth factor receptor 2 (HER2)-targeted humanized monoclonal antibody trastuzumab significantly improves disease- and progression-free survival (PFS), as well as overall survival, in early and metastatic HER2-positive breast cancer [1–4]. Pertuzumab is a novel HER2-targeted humanized monoclonal antibody that binds to the dimerization domain of HER2 [5] and inhibits its heterodimerization with other HER family receptors [6]. Recognizing distinct HER2 epitopes, trastuzumab and pertuzumab, have distinct and complementary mechanisms of action and, in combination, provide a more comprehensive blockade of HER2 signaling compared with either agent individually [7]. Several studies in HER2-positive breast cancer have shown that combining two HER2-targeted therapies—either trastuzumab and pertuzumab [8–10], or trastuzumab and lapatinib (a small-molecule HER2 kinase inhibitor) [11, 12]—improves efficacy compared with a single anti-HER2 agent. Regimens containing both pertuzumab and trastuzumab are well tolerated, and the safety profile of the trastuzumab–pertuzumab combination without chemotherapy is particularly favorable [8–10].

Health-related quality-of-life (HRQoL) is a multidimensional concept encompassing physical, social, emotional, cognitive and role-related well-being, along with the impact of disease-related symptoms, therapy-induced side effects, and even the financial impact of illness. In women with breast cancer, HRQoL may be adversely affected by general cancer-related factors, such as fatigue, pain, and concerns about the illness, along with breast cancer-specific considerations, such as perceived attractiveness or sense of femininity [13]. Because treatment for metastatic

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breast cancer (MBC) is not curative, it is particularly important to demonstrate that any clinical benefits of a novel therapy are not compromised by reductions in HRQoL arising from adverse events or other treatment-related factors. Accordingly, HRQoL data are widely used to inform clinical decision-making, especially in the context of advanced or incurable disease [14–16], and are increasingly being taken into account by investigators when deciding whether to recommend a therapy [17, 18].

In combination with chemotherapy, trastuzumab improves HRQoL in first-line treatment of HER2-positive MBC [19]. However, there is little evidence evaluating HRQoL during dual HER2-targeted therapy [20], and no studies have assessed HRQoL in patients treated with pertuzumab–trastuzumab-based combinations. Assessment of HRQoL was therefore a secondary objective of the CLEOPATRA study, a randomized phase III trial comparing pertuzumab plus trastuzumab plus docetaxel versus placebo plus trastuzumab plus docetaxel as first-line therapy for HER2-positive MBC [21]. Efficacy data from CLEOPATRA demonstrated a significant 6.1-month increase in median PFS in favor of the pertuzumab-containing arm [21], which was accompanied by a significant improvement in overall survival [22]. Most adverse events were mild to moderate and balanced between the two groups, although diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin were more frequent in the pertuzumab arm. Here, we report the HRQoL analysis from CLEOPATRA, which was carried out to determine the impact of pertuzumab on overall patient HRQoL, and to explore whether the prolongation of PFS conferred a clinically meaningful benefit on HRQoL, including increased time to onset or worsening of disease-specific symptoms.

methods

trial design and participants

The CLEOPATRA study (NCT00567190) is a randomized, double-blind, placebo-controlled, phase III trial comparing the efficacy and safety of pertuzumab (PERJETA®, F. Hoffmann-La Roche, Basel, Switzerland; Genentech Inc., South San Francisco, CA) plus trastuzumab plus docetaxel (Taxotere, Sanofi-Aventis, Paris, France) versus placebo plus trastuzumab (Herceptin®, F. Hoffmann-La Roche, Basel, Switzerland) plus docetaxel as first-line treatment of HER2-positive MBC. As reported previously [21], eligible patients were aged ≥18 years, had locally recurrent, unresectable or metastatic HER2-positive breast cancer, and had not received prior chemotherapy or biologic therapy for metastatic disease. HER2 positivity was defined as a centrally confirmed immunohistochemistry 3+ score or fluorescence *in situ* hybridization *HER2*:CEP17 ratio ≥2.0. Patients were also required to have baseline left ventricular ejection fraction of ≥50% and Eastern Cooperative Oncology Group performance status of 0 or 1.

randomization and study treatments

Patients were randomly assigned (1:1) between the two arms. All study medications were administered by intravenous infusion at the start of each 3-week cycle. Pertuzumab or placebo was given at an initial dose of 840 mg, followed by a 420 mg maintenance dose during subsequent cycles. Trastuzumab was administered at 8 mg/kg in the first cycle and 6 mg/kg thereafter. Pertuzumab/placebo and trastuzumab were each given until disease progression or unacceptable toxicity, and no dose modifications were permitted. Docetaxel was administered at 75 mg/m^2, which could be escalated to 100 mg/m^2, if tolerated, or reduced due to toxicity. Discontinuation of docetaxel was only allowed on or before cycle 6 (week 18) due to progressive disease or unacceptable toxicity. Thereafter, further cycles of docetaxel could be administered at the investigator's discretion. Both the groups received a median of eight docetaxel cycles, and the median number of study-treatment cycles per patient in the pertuzumab and placebo arms was 18 and 15, respectively [21].

HRQoL assessments

Female participants completed validated local-language versions of the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire at baseline and within 3 days prior to each 9-weekly tumor assessment until independently determined disease progression. FACT-B is a 37-item HRQoL questionnaire comprising the FACT-General (FACT-G) generic cancer instrument and the disease-specific Breast Cancer Subscale (BCS) [13]. FACT-G evaluates HRQoL across four domains: physical well-being (PWB), social/family well-being, emotional well-being, and functional well-being (FWB). The BCS consists of 10 items addressing symptoms and issues specifically relevant to patients with breast cancer. Respondents rate each item on a four-point scale, from 0 ('not at all') to 4 ('very much'), with higher scores representing better HRQoL. FACT-B has been extensively used and has demonstrated reliability, validity, and sensitivity to change over time [13].

FACT-B responses were used to derive the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) score, which is a composite of PWB, FWB, and BCS domains. The TOI-PFB is commonly used as a clinical trial end point because it is particularly responsive to changes in physical/functional outcomes.

To measure clinically meaningful changes in HRQoL, a minimally important difference (MID) has been defined as the smallest difference in a HRQoL measure that patients perceive as important (beneficial or harmful) [20], and which would lead clinicians to consider a change in patient management. Established MID thresholds are five to six points for the TOI-PFB and two to three points for the BCS [23].

statistical analyses

A prespecified secondary end point of CLEOPATRA was the time from randomization until decline in HRQoL or functioning, as defined by a ≥5-point decrease from baseline in TOI-PFB, which corresponds to the lower limit of the MID for this index. The median time to TOI-PFB decline was estimated using a Kaplan–Meier approach, in which patients lacking observed TOI-PFB decline (including those who died or progressed without TOI-PFB decline) were censored at the last observed assessment date. Patients with a baseline assessment, but with no subsequent assessments available, were censored at day 1. A Cox proportional hazards model, stratified by prior treatment status and region, was used to estimate the hazard ratio (HR) and associated 95% confidence interval (CI) comparing the two arms. The log-rank test was used to compare HRQoL, as measured by time to TOI-PFB decline, between the two treatment arms. A sensitivity analysis was carried out, in which missing data were substituted with the patient's worst observed score. The mean change in TOI-PFB from baseline over time was also summarized graphically.

The same methods were used in *post hoc* exploratory analyses of time to deterioration in breast cancer-specific symptoms, defined by a decline in BCS from a baseline of ≥2 points, which is the lower limit of the MID for this measure.

Time-to-event analyses were based on female patients in the intent-to-treat population, defined as all randomized female patients. The mean changes from baseline over time were based on assessable patients at each time point.

results

patient characteristics

Only female patients completed the FACT-B questionnaire; thus, the HRQoL analysis population included 806 of 808 randomized patients (404 patients in the placebo arm; 402 patients in the pertuzumab arm).

Table. 1. Compliance with completion of the FACT-B questionnaire

	Number of patients with a valid questionnaire out of all eligible patients at scheduled visit, *n*/*N* (%)	
	Placebo + trastuzumab + docetaxel (*n* = 404)	Pertuzumab + trastuzumab + docetaxel (*n* = 402)
Week 9	328/391 (83.9)	314/393 (79.9)
Week 18	304/349 (87.1)	306/375 (81.6)
Week 27	265/319 (83.1)	283/355 (79.7)
Week 36	244/276 (88.4)	253/329 (76.9)
Week 45	188/230 (81.7)	227/285 (79.6)
Week 54	137/179 (76.5)	185/228 (81.1)
Week 63	104/130 (80.0)	160/181 (88.4)
Week 72	82/105 (78.1)	123/147 (83.7)
Week 81	61/79 (77.2)	95/119 (79.8)
Week 90	40/55 (72.7)	72/93 (77.4)
Week 99	25/45 (55.6)	63/71 (88.7)
Week 108	24/36 (66.7)	35/53 (66.0)
Week 117	15/26 (57.7)	25/33 (75.8)
Week 126	12/20 (60.0)	14/21 (66.7)
Week 135	5/10 (50.0)	9/13 (69.2)
Week 144	3/5 (60.0)	5/6 (83.3)
Week 153	0/2 (0.0)	1/2 (50.0)
Week 162	0/2 (0.0)	0/0

FACT-B, Functional Assessment of Cancer Therapy-Breast.

compliance with questionnaire completion

Compliance with completion of the FACT-B questionnaire was at least 75% beyond the first year in both the arms (Table 1). Consistent with the shorter duration of PFS in the placebo group, there was a more rapid decrease in the number of patients eligible for HRQoL assessment in this arm. The percentage of patients completing FACT-B questionnaires at each 9-weekly interval was consistent with the percentage of patients undergoing tumor assessments on the schedule.

HRQoL and functioning: TOI-PFB composite score

During the study, 239 of 402 (59.5%) patients in the pertuzumab arm and 229 of 404 (56.7%) patients in the placebo arm experienced a decrease from baseline of ≥5 points in TOI-PFB composite score of FACT-B. Kaplan–Meier analysis showed a similar time to TOI-PFB decline between the two treatment arms (HR = 0.97; 95% CI, 0.81 to 1.16; $P = 0.7161$), thus demonstrating that the addition of pertuzumab to trastuzumab plus docetaxel did not adversely impact patient HRQoL burden (Figure 1). The median time to TOI-PFB decline was 18.4 weeks in the pertuzumab arm and was 18.3 weeks in the placebo arm, representing approximately six treatment cycles. Comparison of the curves for TOI-PFB decline and time to docetaxel discontinuation indicates that a majority of patients experienced TOI-PFB decline during the period when most were still receiving docetaxel. The clear steps evident in the curves, which correspond to the scheduled 9-weekly intervals, indicate good compliance with the timing of

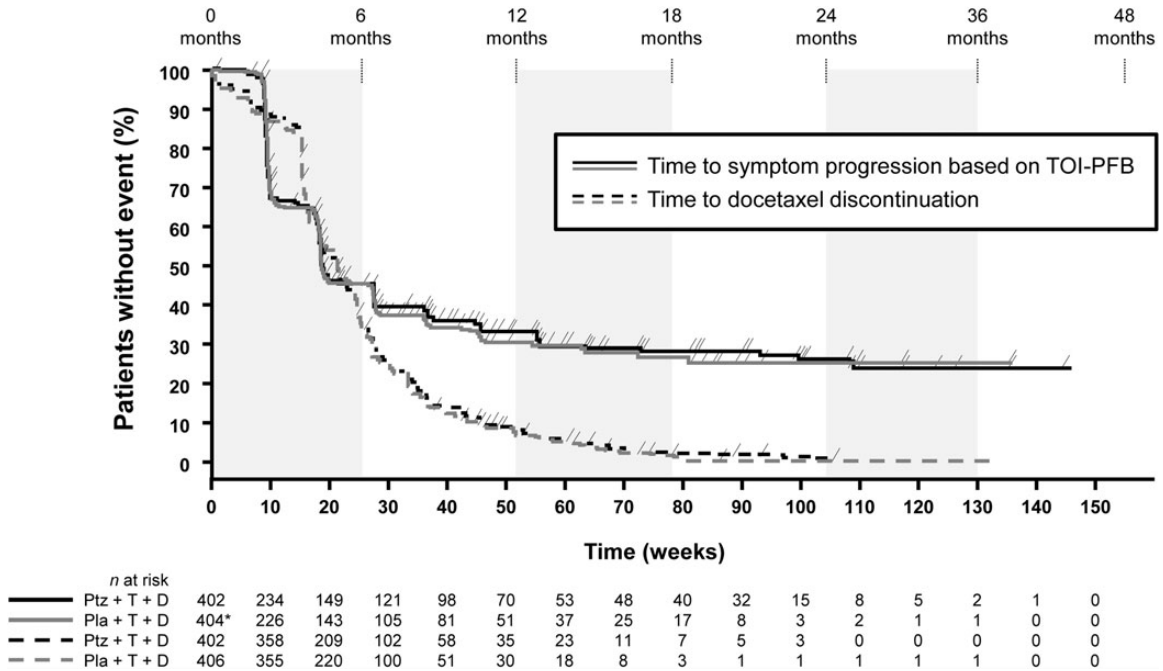

Figure 1. Kaplan–Meier curves of time to ≥5-point reduction from baseline in TOI-PFB and time to docetaxel discontinuation. *There were two male patients in the placebo arm who did not complete the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. D, docetaxel; Pla, placebo; Ptz, pertuzumab; T, trastuzumab; TOI-PFB, Trial Outcome Index-Physical/Functional/Breast.

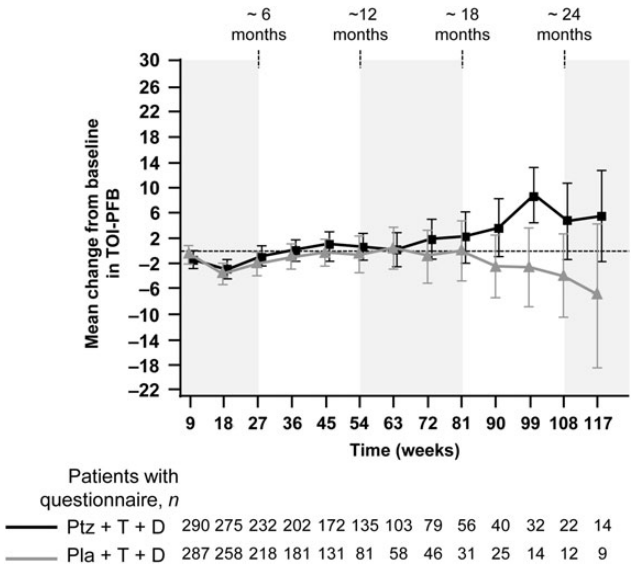

Figure 2. Mean change from baseline in TOI-PFB over time. The graph has been truncated when patient numbers fall below 10 per arm. D, docetaxel; Pla, placebo; Ptz, pertuzumab; T, trastuzumab; TOI-PFB, Trial Outcome Index-Physical/Functional/Breast.

assessments. In a sensitivity analysis in which missing data were replaced with the patient's worst observed score, the time to decline in HRQoL or functioning remained similar between the two arms (HR = 1.01; 95% CI, 0.84 to 1.21; $P = 0.9366$), with the median time to deterioration being 18.1 weeks in both the groups.

Mean baseline TOI-PFB score was 62.2 in the placebo arm and 63.7 in the pertuzumab arm. From baseline to week 18, there were mean reductions in TOI-PFB of –3.5 in the placebo arm versus –3.0 in the pertuzumab arm (Figure 2, supplementary Table S1, available at *Annals of Oncology* online). Mean reductions after week 18 until approximately week 63 were smaller in both groups, suggesting indicating recovery of TOI-PFB scores after initial decline. Mean changes were small and similar until around week 63.

breast cancer-specific symptom deterioration: BCS score

An exploratory *post hoc* analysis was conducted to compare time to decrease from baseline in a BCS score of two or more points between the two study arms [23], which seemed to be reasonable as many clinicians would not wait until symptoms had deteriorated substantially before intervening with another therapy. The median time to deterioration in the BCS domain score was 26.7 weeks in the pertuzumab arm compared with 18.3 weeks in the placebo arm (HR = 0.77; 95% CI, 0.64 to 0.93; $P = 0.0061$), suggesting an improvement in time to BCS decline with pertuzumab treatment. As shown in supplementary Figure S1A, available at *Annals of Oncology* online, the curves tend to separate after ~20–30 weeks. The improvement also applied to all breast cancer symptoms. A sensitivity analysis using a worst-score imputation for patients with missing values also showed a significant benefit in favor of pertuzumab (HR = 0.80; 95% CI, 0.66–0.96; $P = 0.0156$). There was little change in the mean BCS domain score over time in either treatment arm until approximately week 63 (Supplementary Figure S2 and Table S1, available at *Annals of Oncology* online).

discussion

Enhancement or maintenance of HRQoL is increasingly viewed as an important therapeutic goal in MBC management. In the phase III CLEOPATRA study, addition of pertuzumab to trastuzumab plus docetaxel significantly improved both PFS and overall survival in the first-line treatment of HER2-positive MBC [21, 22]. Although adverse event profiles were generally similar between the two arms, some adverse events (e.g. diarrhea and febrile neutropenia) were more frequent in the pertuzumab arm. The present analysis demonstrates that the combination of pertuzumab and trastuzumab with docetaxel had no adverse impact on HRQoL, assessed as time to clinically significant decline in TOI-PFB score, consistent with the clinical benefits of this regimen established in this study. Therefore, the addition of pertuzumab provided patients with an efficacy benefit while maintaining HRQoL.

When comparing HRQoL between the two active regimens that both contain a cytotoxic agent, it is probably unreasonable to anticipate a demonstrable difference, since the quality-of-life picture may be dominated by the adverse effects of chemotherapy. However, exploratory analyses suggested that pertuzumab-containing therapy might significantly prolong time to clinically relevant worsening in breast cancer-specific symptoms. The median time free from BCS deterioration was 8.4 weeks greater with pertuzumab- versus placebo-containing therapy. Nonetheless, this result must be treated with caution given the *post hoc* nature of this TOI-PFB subscale analysis and the low patient numbers at later time points, which increase the likelihood that this is a chance finding. Similarity in mean changes from baseline in FWB and PWB until approximately week 63 suggests that the BCS improvement was not accompanied by deterioration in other TOI-PFB domains (data not shown). The relatively late separation of the BCS curves and their similarity with the PFS curves [21] are consistent with a role for progression in driving BCS decline (Supplementary Figure S1, available at *Annals of Oncology* online). Progression of MBC has been associated with clinically relevant worsening in multiple HRQoL domains and increasing symptom severity [24]. In contrast, effects of toxicity might be expected to manifest earlier.

The mean TOI-PFB scores in both the arms appeared to worsen until approximately week 18 (cycle 6), after which point they recovered back to baseline. This early decline in HRQoL may relate to adverse events of docetaxel, which was administered for a median of eight cycles (24 weeks). Loss of HRQoL during cytotoxic chemotherapy is consistent with previous experience [25]. Support for this explanation is provided by the substantial reduction in the rates of the most common adverse events and the low incidence of grade ≥3 adverse events following docetaxel discontinuation in CLEOPATRA [26]; however, it must be noted that adverse events are not self-reported and so cannot be directly related to patient-reported HRQoL. Interestingly, from week 63, the mean TOI-PFB and BCS appeared to improve in the pertuzumab arm

and worsen in the placebo arm, although these apparent differences must be interpreted with caution, given the low numbers of assessable patients at these later time points.

This is the first study to evaluate HRQoL during dual HER2-targeted therapy with pertuzumab and trastuzumab. Previous studies have demonstrated maintenance or improvement in HRQoL during treatment with a single anti-HER2 agent (trastuzumab or lapatinib), either as monotherapy or alongside a cytotoxic regimen for HER2-positive MBC [19, 27–29]. Furthermore, the addition of trastuzumab to lapatinib had no adverse impact on HRQoL compared with lapatinib alone in a cohort of heavily pretreated patients with HER2-positive MBC that had progressed on trastuzumab-containing therapy [20]. Although there were numerical increases in time to deterioration in FACT-B, FACT-G, TOI-PFB, and BCS scores with trastuzumab plus lapatinib, these did not attain statistical significance.

The present study has several strengths. For each index, we analyzed time to clinically relevant deterioration according to the established MID thresholds, which is likely to provide a more clinically meaningful measure of longitudinal changes in HRQoL in individual patients than a simple change-from-baseline approach. In addition, time to TOI-PFB decline was a predefined secondary end point for which a statistical hypothesis was defined a priori. Compliance with the questionnaire was high; although the proportion of valid responses decreased over time, sensitivity analyses using worst-score imputation support the main conclusions and illustrate the robustness of the findings. One limitation of this study is the lack of follow-up after progression. As a result, the duration of HRQoL follow-up was longer in the pertuzumab arm (due to increased PFS), and we cannot rule out the differences between arms in post-progression HRQoL.

In conclusion, HRQoL outcomes from CLEOPATRA demonstrated that the combination of pertuzumab and trastuzumab plus docetaxel had no adverse effect on overall HRQoL and may prolong time to onset (or worsening) of distressing breast cancer-specific symptoms. These findings are consistent with the established clinical benefits of this regimen as a new option for patients in the first-line treatment of HER2-positive MBC.

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disclosure of prior publication

Preliminary analyses of quality-of-life data from the CLEOPATRA (CLinical Evaluation Of Pertuzumab And TRAstuzumab) trial have been presented as follows:

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disclosure

JC has acted as a consultant for Roche, Celgene, and Novartis and has received honoraria from Roche, Celgene, Novartis, and Eisai. JB has acted as a consultant for Roche. XP has acted as consultant for Roche and GlaxoSmithKline. GR, EC, and AK are employees of Roche Products Ltd, UK. GR has a stock interest in Roche. EC has a stock interest in AstraZeneca. SS received research funding from Roche and is an uncompensated advisor for Roche. YHI and SAI have no conflicts of interest to disclose.

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Informal caregiving to older cancer patients: preliminary research outcomes and implications

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Background: The population of the Western world is aging while cancer survival rates are rising. Older patients with cancer will increasingly be taken care of by informal family caregivers. The current study describes levels of psychological distress, social support and coping abilities reported by partners who are caregivers to older patients with cancer (60+ years), comparing them to a control group of spouses of similarly aged people not suffering from life-threatening illness.
Patients and Methods: Two hundred sixteen partners who are primary caregivers of cancer patients aged 60+ were compared with 76 partners of healthy people aged 60+ and never diagnosed with any terminal illness. Participants completed self-reporting measures on psychological distress, coping ability and social support.
Results: Caregivers to cancer patients reported high levels of distress, low levels of social support and low levels of coping abilities which are negatively correlated to distress. Increased patient age was found to accentuate these processes.
Conclusion: Age and the progression of cancer as a chronic illness present the physician with the reality that focus of care should be on the dyad (patient and caregiver), with high priority given to partners who are informal caregivers.
Key words: cancer, caregiver, coping, distress, old age, social support

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