original articles

Paclitaxel efficacy and toxicity in older women with metastatic breast cancer: combined analysis of CALGB 9342 and 9840

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Background: Two Cancer and Leukemia Group B (CALGB) studies were utilized to determine the efficacy and tolerability of paclitaxel (Taxol) in older patients with metastatic breast cancer.

Patients and methods: CALGB 9840 evaluated weekly paclitaxel (80 mg/m^2) versus paclitaxel every 3 weeks (175 mg/m^2); CALGB 9342 evaluated three doses of paclitaxel as follows: 175, 210 and 250 mg/m^2 each over 3 h every 3 weeks. Of the 1048 patients, paclitaxel was used first line in 57%. The groups: (i) <55 years (45%), (ii) 55–64 years (29%), and (iii) ≥65 years (26%).

Results: Tumor response was also similar among age groups. First-line therapy ($P = 0.0001$) and better performance status (PS) ($P = 0.018$) were significantly related to higher response. Age did not significantly relate to overall survival (OS) or progression-free survival (PFS). First-line therapy, better PS, estrogen receptor positive status and a fewer number of metastatic sites were significantly related to improved OS and PFS. The grade ≥3 toxic effects that increased linearly with age were leucopenia ($P = 0.0099$), granulocytopenia ($P = 0.022$), anorexia ($P = 0.028$), bilirubin elevation ($P = 0.0035$) and neurotoxicity ($P < 0.0001$). Patients over 65 years receiving second-line therapy had the shortest time to neurotoxicity.

Conclusions: Older women with breast cancer derive similar efficacy from treatment with paclitaxel as younger women. Older women are at increased risk for specific toxic effects.

Key words: breast cancer, elderly, geriatric oncology, geriatrics, neurotoxicity, paclitaxel

introduction

Cancer is a disease of aging. The incidence of breast cancer increases with increasing age and almost half of all new breast cancers in the United States now occur in women aged ≥65 years [1, 2]. Systemic adjuvant chemotherapy in women with early-stage breast cancer significantly improves both relapse-free survival and overall survival (OS) for women aged 50–69 years, but there are less data for women aged ≥70 years. Nevertheless, available data suggest that systemic adjuvant chemotherapy may be significantly underused in older patients, even though for many patients in this setting, chemotherapy may improve survival [3]. Furthermore, chemotherapy can also have significant palliative benefit in patients with metastatic breast cancer [4]; however, when chemotherapy is administered to older patients, dose reductions are frequently made that may decrease efficacy [5]. These compromises are explained by the perceived potential for increased chemotherapy-related toxic

effects in older patients. However, data from small trials and retrospective analyses of larger trials suggest that older women in good health tolerate chemotherapy, including anthracycline-based regimens, with toxic effects profiles similar to those of younger patients [6].

Paclitaxel is an integral part of the chemotherapy options for women with breast cancer. It is used in both adjuvant treatment and metastatic disease [6–9]. We conducted a retrospective analysis of two large randomized trials of paclitaxel in the metastatic setting to determine its efficacy and toxicity among different age groups.

patients and methods

A retrospective review was undertaken of Cancer and Leukemia Group B (CALGB) 9840 [8], which evaluated weekly paclitaxel (80 mg/m^2 over 1 h) versus paclitaxel every 3 weeks (175 mg/m^2 over 3 h) and CALGB 9342 [9], which compared three doses of paclitaxel: 175, 210, or 250 mg/m^2 each administered as a 3-h infusion every 3 weeks. CALGB 9342 initially enrolled patients in the second-line setting but was amended to allow patients in the first-line setting. CALGB 9840 accrued patients in both first- and

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second-line treatment. Prior taxane use was allowed if treatment was in the adjuvant setting and had ceased at least 1 year earlier. Adequate hepatic, renal and hematologic parameters were required. Patients receiving trastuzumab (CALGB 9840 only) were required to have a normal baseline left ventricular ejection fraction. Geriatric assessment was not part of the original protocol and information of this type was not recorded. Informed consent was obtained for all patients. Approval for this secondary analysis of the data was obtained from the Cancer and Leukemia Group B Executive Committee.

statistical analysis

The primary end point for the original trials was tumor response; the secondary end points were OS, progression-free survival (PFS) and toxicity. Tumor response was defined as complete or partial remission of breast disease. OS was defined as the time from study entry until death due to any cause. Surviving patients were censored at date of last contact. PFS was defined as the time from study entry until first disease progression or death without progression. Progression-free survivors were censored at the date they were last known to be free from progression. Adverse events that occurred at any time during the course of protocol therapy and that were considered to be related to protocol treatment were graded according to standard National Cancer Institute Expanded Common Toxicity Criteria version 2. We used contingency tables to assess differences between two or more proportions and the Cochran–Armitage test [10] to test for linear trends over three proportions. Time to onset of a specific toxic event was defined as the interval from study entry until estimated date of documented grade 3, 4 or 5 toxicity, whichever grade occurred first. Because adverse events were reported by time intervals rather than at exact dates of onset, the onset date was estimated as the midpoint of the reporting interval. Patients with grade 0–2 severities were censored at the date of last toxicity assessment.

To test for an age effect on response, and OS and PFS, multivariate logistic regression [11] and proportional hazards modeling [12], respectively were used and adjusted for clinical variables of known prognostic importance in metastatic breast cancer. Age was analyzed as a categorical variable (<55 versus 55–64 versus ≥65) using two dummy variables [13]. Other covariates were line of therapy (first versus second) and estrogen receptive (ER) status (positive versus negative), each analyzed as dichotomous variables; body mass index (BMI), defined from the World Health Organization criteria as underweight (<18.5), normal (18.5–24.9) and overweight (≥25) and analyzed as a categorical variable (underweight versus normal versus overweight) using two dummy variables; performance status and disease-free interval (DFI), measured from date of diagnosis of original breast cancer to first recurrence, each analyzed on a continuous scale; and number of sites of metastatic disease at study entry, analyzed on a continuous scale using the square root transformation. Time-to-event variables were estimated using the Kaplan–Meier product limit method. Comparison of two or more distributions used the log-rank test. Unless otherwise stated, all *P*-values are two-sided. Statistical significance is defined as $P \leq 0.05$. Data were extracted from the CALGB database in August 2010.

The effect of trastuzumab was not included in this analysis. The data for human epidermal growth factor receptor 2 (HER-2) status and hence trastuzumab were first collected while CALGB 9840 was already accruing. CALGB 9342 patients did not have HER-2 data collected and data were missing for 290 of the 585 patients on CALGB 9840. When the CALGB 9840 study design was amended mid-trial, patients with HER-2-negative tumors were randomized to paclitaxel with/without trastuzumab, while those with HER-2-positive tumors were required to receive trastuzumab in addition to paclitaxel. Additionally, the weekly dose schedule on CALGB 9840 was found to be significantly superior to the every 3-week schedule. Therefore, 9840 had 10 unique patient subgroups identified by schedule

(weekly and q 3-weekly), HER-2 status (negative, positive and unknown) and trastuzumab (no and yes). The complex relationship among these variables makes direct comparisons difficult. The statistical analysis was carried out by the CALGB Statistical Center.

results

The final sample consisted of all 1048 patients on CALGB 9342 and 9840 who began protocol treatment. The overall median follow-up was 8.8 years (min = 8 days and max = 14 years). At the time of this analysis, 961 (92%) patients had died, 83 were alive and in active follow-up, 1 was lost to follow-up and 3 withdrew consent to be followed. Therapy was received as first-line and second-line treatment by 599 and 449 patients, respectively. Patient demographics by age and line of therapy are given in Table 1. Of the three age categories, the largest proportion of patients were <55 years, and the smallest proportion was ≥65 years. Regardless of age, about two-thirds of the patients were overweight. Nearly all patients had a CALGB performance score of zero or one. Slightly more than half the patient sample had ER-positive tumors. The median DFI was 2 years; one-third had a DFI between 2 and 5 years, and the maximum was 37 years.

tumor response

Table 2 shows tumor response by age and line of therapy. The incidence of tumor response was higher for patients on first-line therapy (37%, 95% confidence interval [CI] = 33% to 41%) than for those on second-line therapy (24%, 95% CI = 20% to 29%); however, response did not differ by patient age group within the first-line setting (36%, 40% and 35%) or within the second-line setting (21%, 30% and 24%), respectively. Results of multivariate logistic regression (Table 3) indicate that age was not associated with tumor response ($P = 0.097$). First line of therapy ($P = 0.0001$) and better performance status ($P = 0.018$) were significantly related to a higher tumor response.

overall survival

First-line therapy, but not patient age, was associated with superior OS. Table 4 shows the multivariate proportional hazards model of selected prognostic variables on OS. After adjusting for line of therapy and other variables, age was not significantly related to OS ($P = 0.73$). First-line therapy ($P < 0.0001$), better performance score ($P < 0.0001$), tumoral ER-positive status ($P < 0.0001$) and fewer metastatic sites ($P = 0.0063$) were all associated with survival benefit.

progression-free survival

As with OS, PFS was longer for patients receiving first-line therapy than for those receiving second-line therapy. PFS did not differ by age. Results of the multivariate proportional hazards model (Table 4) on PFS show that age ($P = 0.31$) did not significantly predict PFS. As with OS, first line of therapy ($P < 0.0001$), better performance status ($P = 0.0061$), positive INS> ER status ($P = 0.0083$) and lower number of metastatic sites ($P = 0.0080$) were each predictive of improved survival.

Table 1. Patient demographics and pretreatment disease-related variables by patient age

Variable	Patient age (years)[a]		
	<55	55–64	≥65
Total patients, n (%)	470 (100)	306 (100)	272 (100)
Study (%)			
9342	44	44	46
9840	56	56	54
Line of therapy (%)			
First	59	58	53
Second	41	42	47
Race (%)			
White	68	77	86
Hispanic	3	3	3
Black	25	18	9
Oriental	11	1	1
Other/missing	2	1	1
Body mass index (%)			
Underweight: <18.5	3	1	3
Normal: 18.5–24.9	33	29	30
Overweight: ≥25	62	69	65
Missing	2	1	2
Performance score (%)			
0	50	45	43
1	43	47	49
2	5	5	7
3	1	1	0
Missing	2	2	1
ER status (%)			
Negative	48	36	34
Positive	45	53	54
Missing	7	12	12
Disease-free interval (%)			
≤2 years	51	43	40
>2 and ≤5 years	36	34	36
>5 years	13	22	24
Missing	1	1	1
Number of met sites (%)			
1–2	53	49	50
3–4	34	38	37
5–8	12	12	11
Missing	1	1	2

ER, estrogen receptor.
[a]137 patients (13%) ≥70 years.

grade ≥3 toxicity

The course of protocol therapy was similar across age groups (Table 5). The median number of cycles delivered was six, six and seven for patients aged <55, 55–64 and ≥65, respectively. Incidence of at least one dose modification (20%, 23% and 24%) and filgrastim use (6%, 5% and 7%) was similar by patient age.

The incidence by age of selected toxic effects of grade 3 or higher severity that occurred any time during the treatment course is shown in Table 5. Of note was the increased incidence in neurotoxicity with increasing age cohort. Neurotoxic events that were assessed and related to increasing age included neurosensory ($P < 0.0001$), neuromotor (i.e. functioning; $P = 0.0002$); neurocortical (i.e. somnolence, agitation;

Table 2. Tumor response (and 95% confidence interval [CI]) by patient age and line of therapy

Line of therapy		Age (years)			Total
		<55	55–64	≥65	
First line	Assessable, N	272	173	144	589
	Response, n (%)	98 (36)	70 (40)	50 (35)	218 (37)
	95% CI (%)	30–42	33–48	27–43	33–41
Second line	Assessable, N	192	128	127	447
	Response, n (%)	41 (21)	38 (30)	30 (24)	109 (24)
	95% CI (%)	16–28	22–38	17–32	20–29

$P = 0.031$) and neurocerebellar (i.e. coordination; $P < 0.0001$). The first onset of serious neurotoxicity could occur at any time over the entire treatment course. Neurotoxicity during first-line treatment developed at a relatively slow rate with a similar incidence at 18 weeks (i.e. after six cycles) among the three age groups: 15% (<55 years), 11% (55–64 years) and 12% (≥65 years). Overall, patients receiving second-line treatment experienced neurotoxicity sooner than patients receiving first-line treatment with those on second-line therapy who were ≥65 years having the shortest time to neurotoxicity onset compared with patients <65 (Figure 1). Of patients receiving second-line therapy, age differences in neurotoxicity were first observed after three cycles (9 weeks) when the incidence of grade ≥3 neurotoxicity was 25% for the ≥65 group compared with 10% and 15% for the two younger groups. By 18 weeks (six cycles), the incidence had risen to 35% compared with 12% and 20%, respectively.

We also observed age-related differences for hematologic toxic effects with the incidence of leucopenia ($P = 0.0099$) and granulocytopenia ($P = 0.022$) increasing with increasing age. In contrast to the relatively constant rate of neurotoxicity onset, the probability of developing myelosuppression was highest after the first dose of therapy (3 weeks), and thereafter plateaued, perhaps due to the use of hematopoietic growth factors and/or dose reduction. Compared with patients on first-line treatment, a considerably higher incidence of patients on second-line treatment experienced hematologic toxicity during the first cycle. Also, patients aged ≥65 who received second-line treatment had the highest probability of experiencing either hematologic toxicity.

The incidence of anorexia ($P = 0.028$), hyperbilirubinemia ($P = 0.0035$) and malaise ($P = 0.0028$) were also highest in the older patients. The incidence of hyperglycemia was not increased in older patients.

discussion

In the current analysis, benefit from treatment was associated with known prognostic factors, namely, performance status and line of therapy, but not patient age. This is consistent with [14, 15] clinical trials in other solid tumors showing that older patients derive the same benefit as younger patients. We observed an increased incidence of several paclitaxel-related toxic effects that were age related and more frequent in older patients. This observation was most striking for several neurotoxicities, including neurosensory, neuromotor and

Table 3. Observed effect of age on tumor response (N = 913, tumor response = 33%)

Variable	Comparison for OR, more : less likely to respond	OR	95% confidence nterval for OR	P-value
Age	<55 : ≥65	1.03	0.72–1.48	0.097
	55–64 : ≥65	1.38	0.94–2.02	
Line of therapy	First : Second	2.03	1.51–2.73	0.0001
DFI	1 : 5[a]	1.05	0.89–1.25	0.56
Performance score	1 : 2[a]	1.35	1.05–1.73	0.018
Tumoral ER status	Negative : positive	1.01	0.75–1.35	0.98
Number of metastatic sites	2 : 5[a]	1.13	0.84–1.51	0.42
BMI	Underweight : normal	1.35	0.43–4.24	0.26
	Overweight : normal	1.26	0.92–1.71	

BMI, body mass index; DFI, disease-free interval; ER, estrogen receptor; OR, odds ratio.
[a]These variables were analyzed on a continuous scale; exact numbers are provided as examples for the OR.

Table 4. Observed effect of age on OS and PFS (N = 921; 91% OS and 95% PFS events)

Variable	Comparison for HR, worse : better	OS			PFS		
		HR	95% CI for HR	P-value	HR	95% CI for HR	P-value
Age	<55 : ≥65	1.07	0.90–1.27	0.73	1.14	0.96–1.35	0.31
	55–64 : ≥65	1.04	0.86–1.25		1.08	0.90–1.30	
Line of therapy	Second : First	1.85	1.61–2.13	<0.0001	1.52	1.32–1.74	<0.0001
DFI	1: 5[a]	1.02	0.93–1.11	0.69	1.01	0.93–1.11	0.75
Performance score	2 : 1[a]	1.37	1.22–1.55	<0.0001	1.18	1.05–1.32	0.0061
Tumoral ER status	Negative : Positive	1.53	1.33–1.76	<0.0001	1.20	1.05–1.39	0.0083
Number of metastatic sites	5: 2[a]	1.22	1.06–1.40	0.0063	1.20	1.05–1.38	0.0080
BMI	Normal : underweight	1.17	0.73–1.87	0.11	1.09	0.69–1.74	0.47
	Normal : overweight	1.17	1.01–1.36		1.09	0.95–1.26	

BMI, body mass index; CI, confidence interval; DFI, disease-free interval; ER, estrogen receptor; HR, hazard ratio; OR, odds ratio; OS, overall survival; PFS, progression-free survival.
[a]These variables were analyzed on a continuous scale; exact numbers are provided as examples for the HR.

central nervous system (neurocortical and neurocerebellar) side-effects and occurred in both the first- and second-line settings. The onset of grade 3 or higher neurotoxicity occurred sooner for patients on second-line treatment aged ≥65 years than for younger second-line patients and for all patients on first-line treatment.

The incidence of anorexia, malaise, hyperbilirubinemia and hematologic toxicity (leucopenia and granulocytopenia) also increased with increasing age but there was no age-related difference in infection. As noted in other studies, and regardless of age, the probability of developing hematologic toxicity was greatest by the end of the first cycle of treatment. Compared with patients on first-line treatment, proportionally more patients on second-line treatment experienced hematologic toxicity.

Paclitaxel is an important part of chemotherapy regimens for a number of malignancies, particularly breast, lung and gynecologic cancers. A prospective trial demonstrated age-related differences in the pharmacokinetics of paclitaxel but no significant adverse sequelae in terms of infectious complications and hospitalization [13]. This trial analyzed only the first cycle of treatment; therefore, cumulative toxicity was not assessed. This report provides more extensive data during an entire course of treatment. The Gruppo Italiano di Oncologia Geriatrica (GIOGer) reported a trial of weekly paclitaxel in elderly patients with breast cancer. This prospective study included a baseline geriatric assessment (GA). They demonstrated efficacy but an increase in cardiovascular toxicity. The GA predicted a lower probability of response and survival but not of toxicity. Their analysis was likely limited by a relative small number of patients (n = 46) [16].

Paclitaxel has rarely been associated with central nervous system toxic effects [17]. It is difficult to assess whether the increase noted in older patients is related to the chemotherapy or less likely to the effect of short acting premedication (dexamethasone and diphenhydramine). The neurosensory and neuromotor toxic effects observed are particularly significant in the older population and can potentially lead to loss of mobility, increased falls and other disability. The increased risk of neuropathy in older patients has not been consistently observed in clinical trials [6, 15]. This may be due to excluding patients with preexisting significant neuropathy or possibly lack of reporting [17]. Age itself may not be a risk factor but the additional comorbidities such as diabetes may be the predisposing factor [18]. In view of this, older patients should

Table 5. Course of protocol treatment by patient age

	Patient age (years)			P-value
	<55	55–64	≥65	
Number of patients treated, N (%)	470 (100)	306 (100)	272 (100)	
Number of patients with Rx and AE data, n (%)	465 (99)	302 (99)	270 (99)	
Treatment				
Number of cycles received, Median (range)	6 (1–72)	6 (1–55)	7 (1–44)	NS
Number of patients dose modified, n (%) (95% CI [%])	91 (20) (16–23)	68 (23) (18–28)	65 (24) (19–30)	NS
If dose modified, Number of cycles modified, Median (range)	1 (1–8)	1 (1–9)	1 (1–3)	NS
Number of Patients received G-CSF, n (%) (95% CI)	26 (6) (4–8)	16 (5) (3–8)	20 (7) (5–11)	NS
If received G-CSF, Number of cycles G-CSF, Median (range)	2 (1–23)	2 (1–7)	1 (1–14)	NS
Adverse events, grade 3 or higher (%)				[a]
WBC	21	25	30	0.0099
Granulocytes	35	35	44	0.022
Anorexia	1	1	3	0.028
Bilirubin	<1	1	3	0.0035
Neurosensory	17	18	28	<0.0001
Neuromotor	5	8	14	0.0002
Neurocortical	1	1	3	0.031
Neurocerebellar	0	1	3	<0.0001
Malaise	4	6	10	0.0028
Prothrombin time	<1	3	0	0.013[b]
Eye	<1	0	1	0.015[b]

NS, not significant (i.e. P-value >0.05); G-CSF, filgrastim.
[a]Unless otherwise indicated, P-value for tests on AE is from test for linear trend.
[b]From chi-square test for differences in proportions.
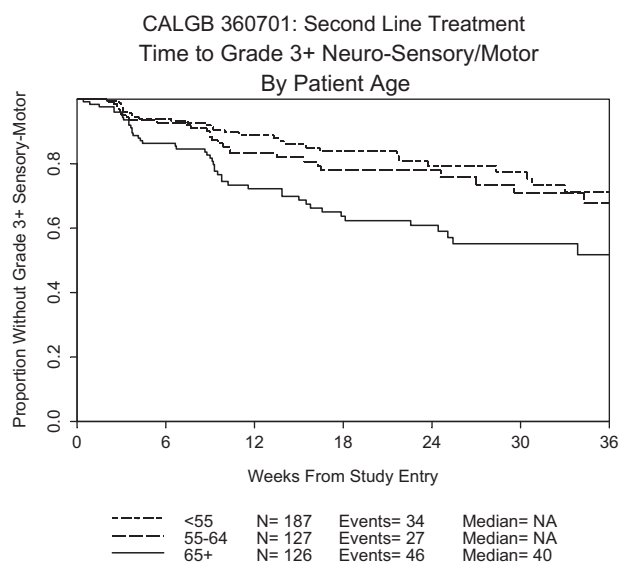
Figure 1. CALGB 360701: second-line treatment. Second-line therapy and time to grade 3 or more neurotoxicity.

be closely monitored for neurotoxicity to minimize complications.

The elderly patient may have a different spectrum of dose-limiting toxicity than a younger patient and common toxicity criteria as currently used may not be adequate to assess adverse events in elderly patients. For example, assessment of neuropathy in elders should include evaluation of functional decline and falls. The reporting of toxicity in large clinical trials should include a subset analysis of older patients. It is often unclear whether a specific group of patients in a trial bears the burden of toxicity. Most trials only report grade 3/4 toxicity; grade 2 toxicity in an older patient often has clinical relevance. It will help clinicians in decision making if they know the full spectrum of toxicity. This combined analysis further confirms that older patients who are eligible for clinical trials derive the same benefit as younger patients and can be treated safely [19]. Paclitaxel has been shown to be tolerable in the elderly with efficacy and safety [13, 16, 20]. These data suggest that paclitaxel is as effective in carefully selected older as in younger patients with metastatic breast cancer. The increased risk of

neurotoxicity in elders is of concern and older patients should be closely monitored for this event.

disclosure

The authors declare no conflicts of interest.

references

1. Klepin H, Mohile S, Hurria A. Geriatric assessment in older patients with breast cancer. J Natl Compr Canc Netw 2009; 7: 226–236.
2. Crivellari D, Aapro M, Leonard R et al. Breast cancer in the elderly. J Clin Oncol 2007; 25: 1882–1890.
3. Bouchardy C, Rapiti E, Blagojevic S et al. Older female cancer patients: importance, causes, and consequences of undertreatment. J Clin Oncol 2007; 25: 1858–1869.
4. Holmes HM. Rational prescribing for patients with a reduced life expectancy. Clin Pharmacol Ther 2009; 85: 103–107.
5. Dixon DO, Neilan B, Jones S et al. Effect of age on therapeutic outcome in advanced diffuse histocytic lymphoma: the Southwest Oncology Group experience. J Clin Oncol 1986; 4: 295–305.
6. Muss HB, Berry DA, Cirrincione C et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B experience. J Clin Oncol 2007; 25: 3699–3704.
7. Citron ML, Berry DA, Cirrincione C et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003; 21: 1431–1439.
8. Seidman AD, Berry D, Cirrincione C et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 2008; 26: 1642–1649.
9. Winer EP, Berry DA, Woolf S et al. Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: Cancer and Leukemia Group B trial 9342. J Clin Oncol 2004; 22: 2061–2068.
10. Agresti A, Mehta CR, Patel NR. Exact inference for contingency tables with ordered categories. J Am Stat Assoc 1990; 85: 453–458.
11. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: Wiley 1989.
12. Cox DR. Regression models and life tables. J Royal Stat Soc 1972; 34: 187–220.
13. Lichtman SM, Hollis D, Miller AA et al. Prospective evaluation of the relationship of patient age and paclitaxel clinical pharmacology: Cancer and Leukemia Group B (CALGB 9762). J Clin Oncol 2006; 24: 1846–1851.

14. Muss HB, Woolf S, Berry D et al. Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA 2005; 293: 1073–1081.

15. Goldberg RM, Tabah-Fisch I, Bleiberg H et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. J Clin Oncol 2006; 24: 4085–4091.

16. Del Mastro L, Perrone F, Repetto L et al. Weekly paclitaxel as first-line chemotherapy in elderly advanced breast cancer patients: a phase II study of the Gruppo Italiano di Oncologia Geriatrica (GIOGer). Ann Oncol 2005; 16: 253–258.

17. Langer CJ, Manola J, Bernardo P et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of eastern

cooperative oncology group 5592, a randomized trial. J Natl Cancer Inst 2002; 94: 173–181.

18. Rowinsky EK, Chaudhry V, Cornblath DR, Donehower RC. Neurotoxicity of Taxol. J Natl Cancer Inst Monogr 1993; 107–115.

19. Kumar A, Soares HP, Balducci L, Djulbegovic B. Treatment tolerance and efficacy in geriatric oncology: a systematic review of phase III randomized trials conducted by five National Cancer Institute-sponsored cooperative groups. J Clin Oncol 2007; 25: 1272–1276.

20. Hilpert F, du Bois A, Greimel ER et al. Feasibility, toxicity and quality of life of first-line chemotherapy with platinum/paclitaxel in elderly patients aged >or = 70 years with advanced ovarian cancer—a study by the AGO OVAR Germany. Ann Oncol 2007; 18: 282–287.