Imaging, Diagnosis, Prognosis

Serum Lactate Dehydrogenase Is Prognostic for Survival in Patients with Bone Metastases from Breast Cancer: A Retrospective Analysis in Bisphosphonate-Treated Patients

Janet E. Brown[1,2], Richard J. Cook[3], Allan Lipton[4], and Robert E. Coleman[2]

Abstract

Purpose: Survival is highly variable in women with bone metastases from breast cancer and prognostic factors are needed. We analyzed data from a phase III trial comparing zoledronic acid (ZOL) with pamidronate in patients with breast cancer and bone metastases to identify variables prognostic for overall survival.

Experimental Design: Patients who received ZOL ($n = 435$) with bone marker assessments and complete baseline data were included. Relative risks (RR) of death over 24 months were assessed using a stratified Cox regression analysis. A reduced model was generated using stepwise backward elimination until only significant ($P < 0.05$) variables remained.

Results: Only 5 of 19 variables analyzed remained significantly prognostic for survival in the reduced multivariate model. These included age more than 50 years (RR 1.78–2.53, $P \leq 0.01$ for each decade >50 versus ≤50); Functional Assessment of Cancer Therapy-General (FACT-G) score less than 65 units ($P < 0.05$ vs. ≥75 units); impaired (PS ≥ 1) versus fully active (PS = 0) Eastern Cooperative Oncology Group (ECOG) performance status (RR 1.74, $P < 0.01$); prior versus no prior chemotherapy (RR 1.97; $P < 0.01$), and lactate dehydrogenase (LDH) levels. Lactate dehydrogenase ≥ upper limit of normal (ULN) but < 2 × ULN correlated with a two-fold increased risk of death, and LDH > 2 × ULN correlated with a six-fold increased risk of death versus LDH < ULN ($P < 0.0001$ for both). Baseline bone marker levels were not significantly correlated with survival after adjustment for other significant covariates.

Conclusions: This retrospective analysis shows that LDH levels correlate strongly with survival in patients with bone metastases from breast cancer and confirms the relevance of previously described prognostic factors. *Clin Cancer Res; 18(22); 6348–55. ©2012 AACR.*

Introduction

Among patients with advanced breast cancer, approximately 65% to 75% will develop bone metastases (1), which weaken the structural integrity of the skeleton and can result in painful and potentially disabling skeletal-related events (SRE) including pathologic fracture, the need for radiotherapy or surgery to bone, spinal cord compression, and hypercal-cemia of malignancy. Overall, SREs have been associated with reduced performance status, impaired health-related quality of life, shortened survival, and increased bone pain (2, 3).

There is ongoing interest in identifying prognostic variables that could predict a patient's risk for disease progression and death. For example, age, clinical status of nodes, tumor size, race, and number of positive nodes have been reported as prognostic factors for survival in patients with breast cancer that is limited to local or regional sites (4). More recently, factors such as human epidermal growth factor receptor-2 (HER2) expression have been strongly associated with overall survival (OS) prognosis (5), and there has been considerable progress in the development of gene-expression–based prognosis for survival (6). In addition, the identification of circulating tumor cells (CTC) has been approved as a prognostic marker to assess response to treatment in patients with metastatic breast cancer (7), and the CellSearch (Quest Diagnostics) assay for CTCs is claimed to be a strong, independent predictor of OS, and progression-free survival. Among women with bone metastases from breast cancer, median survival is approximately 2 to 3 years (8), in comparison with the 12- to 18-month median survival in patients with liver metastases (9). Unfortunately, specific prognostic models for long-term survival in patients with bone metastases from

Authors' Affiliations: [1]Cancer Research UK Experimental Cancer Medicine Centres at Leeds and Sheffield; [2]Cancer Research Centre, Academic Unit of Clinical Oncology, Weston Park Hospital, Sheffield; [3]University of Waterloo, Waterloo, Ontario, Canada; and [4]Milton S. Hershey Medical Center, Penn State University, Hershey, Pennsylvania

Corresponding Author: Janet E. Brown, Cancer Research UK Clinical Centre, Leeds, JIF Building, St. James' University Hospital, Becket Street, Leeds LS9 7TF, United Kingdom. Phone: 44-113-206-4184; Fax: 44-113-246-0136; E-mail: j.e.brown@leeds.ac.uk

Translational Relevance

Survival is highly variable in women with bone metastases from breast cancer, and prognostic factors are needed. This retrospective exploratory analysis assessed data from a phase III trial comparing zoledronic acid with pamidronate in patients with breast cancer and bone metastases to identify variables prognostic for overall survival. Results from this analysis show that lactate dehydrogenase (LDH) levels correlate strongly with survival in patients with bone metastases from breast cancer. Furthermore, this analysis also confirms the relevance of previously described prognostic factors such as age, Eastern Cooperative Oncology Group performance status, prior chemotherapy, and Functional Assessment of Cancer Therapy-General (FACT-G) score. On the basis of the current study, the combination of LDH with other prognostic factors into a weighted prognostic score for survival in patients with bone metastases from breast cancer would be a valuable next step.

breast cancer are not well developed (10–14). We have previously shown that elevated baseline levels of the biochemical marker N-telopeptide of type I collagen (NTX) were associated with an increased risk of SREs (15, 16), and normalization of NTX levels correlated with reduced risks of fracture, SREs, and death versus persistently elevated NTX after 3 months of treatment with zoledronic acid (ZOL; refs. 17, 18). Factors such as prior SRE, number of bone lesions, and the severity of bone pain may also provide insight about SRE risk (19, 20). Because a range of systemic treatments is now available and many patients with breast cancer will survive for several years after diagnosis of bone metastases, it is important to identify factors that are prognostic for survival to tailor treatments accordingly.

The phase III, randomized, controlled trial comparing ZOL with pamidronate in patients with bone metastases from breast cancer (21, 22) generated an extensive database of baseline clinical and biochemical parameters with long-term (25-month) clinical follow-up that can be used for correlative analyses (23). A recent multivariate analysis of baseline variables in this trial identified prognostic factors for SRE risk including age, pain score, prior history of an SRE, predominant lesion type, elevated bone-specific alkaline phosphatase (BSAP), and elevated lactate dehydrogenase (LDH; ref. 24). The current exploratory analysis uses data collected prospectively in the above trial and was conducted to investigate prognostic variables for OS among patients with bone metastases from breast cancer enrolled in the ZOL arm of the pamidronate-controlled trial.

Materials and Methods

Patient population

Data were obtained for patients with bone metastases from breast cancer who were enrolled (October 1998 to December 1999) in the international, randomized, phase III trial comparing ZOL with pamidronate (21–23). All patients had at least 1 radiographically confirmed bone lesion, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2, serum creatinine 3 mg/dL (265 μmol/L) or more, and no prior bisphosphonate therapy. In this trial, patients were randomized to pamidronate (90 mg every 3–4 weeks) or either of 2 ZOL treatment arms (4 mg or 8 mg every 3–4 weeks) for up to 2 years. During the trial, the ZOL 8-mg dose was reduced to 4 mg for renal safety and is referred to as the 8/4-mg group. All patients enrolled in the trial provided written informed consent. To preserve homogeneity of bisphosphonate treatment and because of the large numbers of patients available, only patients with breast cancer in the ZOL treatment groups were included in the analyses reported herein. In the subset of patients who enrolled in North American treatment centers, all baseline prognostic factors including biochemical markers of bone turnover (e.g., BSAP and NTX) were assessed at baseline and at months 1, 3, 6, and 12 of the study.

Laboratory procedures

Laboratory samples were collected and processed locally on study enrollment at the baseline visit according to the strict standard operating procedures (SOP) set by the study. Sample storage and shipping to regional GCP-accredited central laboratories (Mayo Medical Laboratories in North and South America; BARC in Europe, Australia, and South Africa) also adhered to the study SOPs. Samples were analyzed as per guidelines set by each regional central laboratory. Patient baseline samples for laboratory analysis were measured at the time of enrollment, not at the time of bone metastasis diagnosis.

Statistical analyses

Patients with breast cancer who received ZOL (both the 4-mg and 8/4-mg groups) who also had assessments of biochemical markers of bone metabolism and complete data sets of baseline variables ($n = 435$) were included in the statistical models. Nineteen baseline variables with potential prognostic value, including age, race, weight, predominant radiographic appearance of bone lesion(s)—osteolytic, osteoblastic, and other—Functional Assessment of Cancer Therapy-General (FACT-G) score, ECOG PS, history of SRE, history of chemotherapy, concomitant endocrine therapy, presence of extraskeletal metastases (with this variable being subdivided into liver and nonliver metastases as it was possible that patients with liver metastases may have a different survival pattern compared with those with other extraskeletal metastases), NTX, BSAP, lymphocyte count, hemoglobin, serum glutamic oxaloacetic acid, albumin, creatinine, and total serum LDH, were included in the univariate and full multivariate Cox regression models to assess relative risk and associated 95% confidence intervals (CI) for death throughout the 24-month trial.

All models were stratified based on time since diagnosis of primary cancer (<5 vs. ≥5 years) and by ZOL treatment group. Patient age was categorized into <50, ≥50 to <60, ≥60 to <70, and ≥70 years of age. Patient weight was categorized

into <60, ≥60 to <70, ≥70 to <80, and ≥80 kilograms. Patient FACT-G score was categorized into <65, ≥65 to <75, ≥75 to <90, and ≥90 units. At the time this trial was conducted, HER2 and estrogen receptor status of the primary tumor were not routinely assessed. Laboratory values (including bone marker levels) were treated as dichotomous variables using either the established upper limit of normal (ULN) as the cut-off point or the respective ULN from each specific laboratory for each patient's assessments; the only exception was for hemoglobin, where the median value of 12 g/dL was used. Serum LDH levels were categorized into 3 different levels using laboratory specific (because of variations in this international trial, absolute cut-off values would have been less appropriate) ULN and $2 \times$ ULN as cut-off points (i.e., LDH < ULN; ULN ≤ LDH < $2 \times$ ULN; LDH ≥ $2 \times$ ULN). All other variables were treated as dichotomous (yes vs. no).

For all analyses, associations were considered statistically significant if their associated P value was <0.05. Reduced multivariate models were generated by stepwise backward elimination until only significant ($P < 0.05$) variables remained. Kaplan–Meier estimates were computed to graphically summarize the distribution of time to death stratified by newly identified prognostic variables.

Results

Patients

Among patients with bone metastases from breast cancer enrolled in the phase III trial comparing ZOL with pamidronate ($N = 1,130$), a total of 742 patients were randomized to the 2 ZOL arms of the study (ref. 22; Table 1; ref. 24). The majority of patients (81%) were less than 70 years of age, had some impairment in ECOG-PS (65%), had a prior SRE (59%), and had received prior chemotherapy (76%). Among the 742 patients in the ZOL arms, a complete baseline assessment for all 19 variables of interest was available for 435 patients, who were therefore included in the models described below. The median time from diagnosis of bone metastasis to study entry was 3.75 months.

Univariate and multivariate models of overall survival

Risk factors that could potentially influence OS were evaluated in univariate analyses for each of the 19 baseline quartile-based categorical and dichotomous variables. Among these variables, 15 were found to be associated with a significant increase in the risk of death, including low weight, low FACT-G score, ECOG PS ≥ 1, prior SRE, prior chemotherapy, concomitant hormone therapy, metastases, osteoblastic lesions, elevated NTX, elevated BSAP, elevated hemoglobin, elevated aspartate aminotransferase (AST), elevated albumin, and elevated LDH (Table 2). The remaining variables (age, race, lymphocyte counts, and serum creatinine) were not significantly associated with increased risk of death.

However, only 5 covariates were significantly associated with increased risk of death after adjustment for all other variables in the full multivariate model. These included advanced age, low FACT-G score, ECOG PS ≥ 1, prior chemotherapy, and elevated LDH (Table 2), with LDH

Table 1. Baseline demographics and laboratory values

Variable (evaluable patients, *n*)	Patients, *n* (%)
Age, y	N = 742
0 to <50	207 (28)
≥50 but <60	213 (29)
≥60 but <70	181 (24)
≥70	141 (19)
Duration of cancer at study entry, y	N = 742
<5	375 (51)
≥5	367 (49)
ECOG PS	N = 740
Fully active (PS = 0)	256 (35)
Some impairment (PS ≥ 1)	484 (65)
Prior SRE	N = 740
No	302 (41)
Yes	438 (59)
History of chemotherapy	N = 734
No	179 (24)
Yes	555 (76)
NTX, nmol/mmol creatinine	N = 490
<64	197 (40)
≥64	293 (60)
BSAP, U/L	N = 501
<146	130 (26)
≥146	371 (74)
Hemoglobin, g/dL	N = 729
≤12	364 (50)
>12	365 (50)
AST, U/L	N = 735
<ULN	446 (61)
≥ULN	289 (39)
Albumin, g/L	N = 735
≤35	94 (13)
>35	641 (87)
Creatinine, mg/dL	N = 735
<ULN	387 (53)
≥ULN	348 (47)
LDH, U/L	N = 735
<ULN	537 (73)
≥ULN	198 (27)

NOTE: Adapted with kind permission from Springer Science+Business Media: Prognostic factors for skeletal complications from metastatic bone disease in breast cancer. 123, 2010, page 770, Brown JE, Lipton A, Costa L, and Coleman R. Table 1.

being the only statistically significant laboratory parameter. The 5 variables that were associated with a statistically significant increase in risk of death remained significant covariates after applying stepwise backward elimination of all nonsignificant variables in the multivariate model (Fig. 1). In the reduced model, elevated LDH [a factor previously identified as a prognostic marker in other cancers (25–29), but not specifically in patients with advanced

Table 2. Univariate and multivariate models for overall survival in patients with bone metastases from breast cancer

Factor	Univariate			Full multivariate		
	RR	95% CI	P	RR	95% CI	P
Versus age < 50 years						
50 y ≤ age < 60 y	1.359	0.932–1.981	0.1110	1.795	1.174–2.746	**0.0069**
60 y ≤ age < 70 y	1.122	0.753–1.674	0.5710	1.598	1.010–2.526	**0.0450**
70 y ≤ age	1.494	0.996–2.241	0.0523	2.472	1.533–3.988	**0.0002**
Global test			0.1857			**0.0020**
Versus weight ≥ 80 kg						
Weight < 60 kg	1.816	1.243–2.654	**0.0020**	1.590	1.044–2.420	**0.0306**
60 kg ≤ weight < 70 kg	0.929	0.636–1.356	0.7020	0.934	0.625–1.394	0.7379
70 kg ≤ weight < 80 kg	0.922	0.614–1.384	0.6941	1.022	0.663–1.576	0.9205
Global test			**0.0008**			0.0560
Versus FACT-G < 65 units						
65 units ≤ FACT-G < 75 units	0.713	0.483–1.053	0.0894	0.700	0.457–1.073	0.1017
75 units ≤ FACT-G < 90 units	0.645	0.452–0.920	**0.0154**	0.606	0.410–0.895	**0.0119**
90 units ≤ FACT-G	0.442	0.296–0.659	**<0.0001**	0.540	0.344–0.845	**0.0071**
Global test			**0.0008**			**0.0282**
ECOG PS ≥ 1 vs. 0	2.216	1.608–3.052	**<0.0001**	1.572	1.097–2.253	**0.0137**
Versus white race						
Black/Asian/other	1.152	0.778–1.705	0.4809	0.924	0.602–1.418	0.7170
≥1 Prior SRE vs. 0	1.396	1.044–1.868	**0.0246**	1.130	0.812–1.572	0.4677
Prior chemotherapy (≥1 vs. 0)	1.779	1.223–2.586	**0.0026**	1.812	1.169–2.808	**0.0078**
Concomitant HT (yes vs. no)	0.600	0.449–0.801	**0.0005**	0.938	0.673–1.308	0.7063
Metastases sites						
≥1 liver vs. 0 on liver	1.760	1.288–2.404	**0.0004**	1.153	0.819–1.624	0.4148
≥1 lung/brain/other vs. 0	1.463	1.103–1.940	**0.0082**	1.272	0.930–1.741	0.1321
Predominant lesion (vs. osteolytic)						
Osteoblastic	0.679	0.499–0.923	**0.0136**	0.794	0.575–1.096	0.1599
Other	0.690	0.476–1.000	**0.0500**	0.659	0.447–0.970	**0.0344**
Global test			**0.0250**			0.0847
NTX ≥ 64 vs. < 64 nmol/mmol creatinine	1.627	1.213–2.183	**0.0012**	1.151	0.827–1.603	0.4055
BSAP ≥ 146 vs. < 146 U/L	1.596	1.135–2.244	**0.0072**	1.084	0.733–1.602	0.6866
Lymphocytes ≥ ULN vs. < ULN	0.649	0.341–1.237	0.1890	0.967	0.489–1.913	0.9225
Hemoglobin ≥ 12 vs. < 12 g/dL	0.678	0.512–0.897	**0.0066**	0.901	0.659–1.233	0.5148
AST ≥ ULN vs. < ULN	1.931	1.466–2.543	**<0.0001**	1.212	0.852–1.725	0.2846
Serum albumin ≥ 35 vs. < 35 g/L	0.460	0.316–0.670	**<0.0001**	0.780	0.503–1.212	0.2693
Serum creatinine ≥ ULN vs. < ULN	0.884	0.659–1.185	0.4087	1.092	0.787–1.515	0.5994
Versus LDH < ULN						
ULN ≤ LDH < 2 × ULN	2.190	1.593–3.011	**<0.0001**	1.563	1.042–2.344	**0.0307**
2 × ULN ≤ LDH	5.188	2.965–9.077	**<0.0001**	4.503	2.269–8.935	**<0.0001**
Global test			**<0.0001**			**<0.0001**

Abbreviations: HT, hormone therapy; RR, risk ratio.

breast cancer and bone metastases] showed a strong correlation with risk of death. Patients with LDH levels ≥ 2 × ULN had an almost 6-fold increased risk of death compared with patients whose LDH levels were below the ULN (RR 5.937; P < 0.0001).

LDH as a prognostic marker of survival in advanced breast cancer

Using the ULN and 2 × ULN as cutoff points, the resulting 3 LDH populations had significantly different survival, and between-group differences were apparent throughout the course of the study (P < 0.0001; Fig. 2). Patients with LDH levels < ULN had the best OS, and approximately 65% of patients were still alive at 24 months' follow-up. In contrast, the median survival among patients with LDH levels ≥ ULN but <2 × ULN was approximately 17 months, and those patients with LDH levels ≥2 × ULN had the worst OS (median ∼5 months). At the 12-month time point, Cox regression analyses showed that significant prognostic factors predictive of >30% risk of death included high LDH,
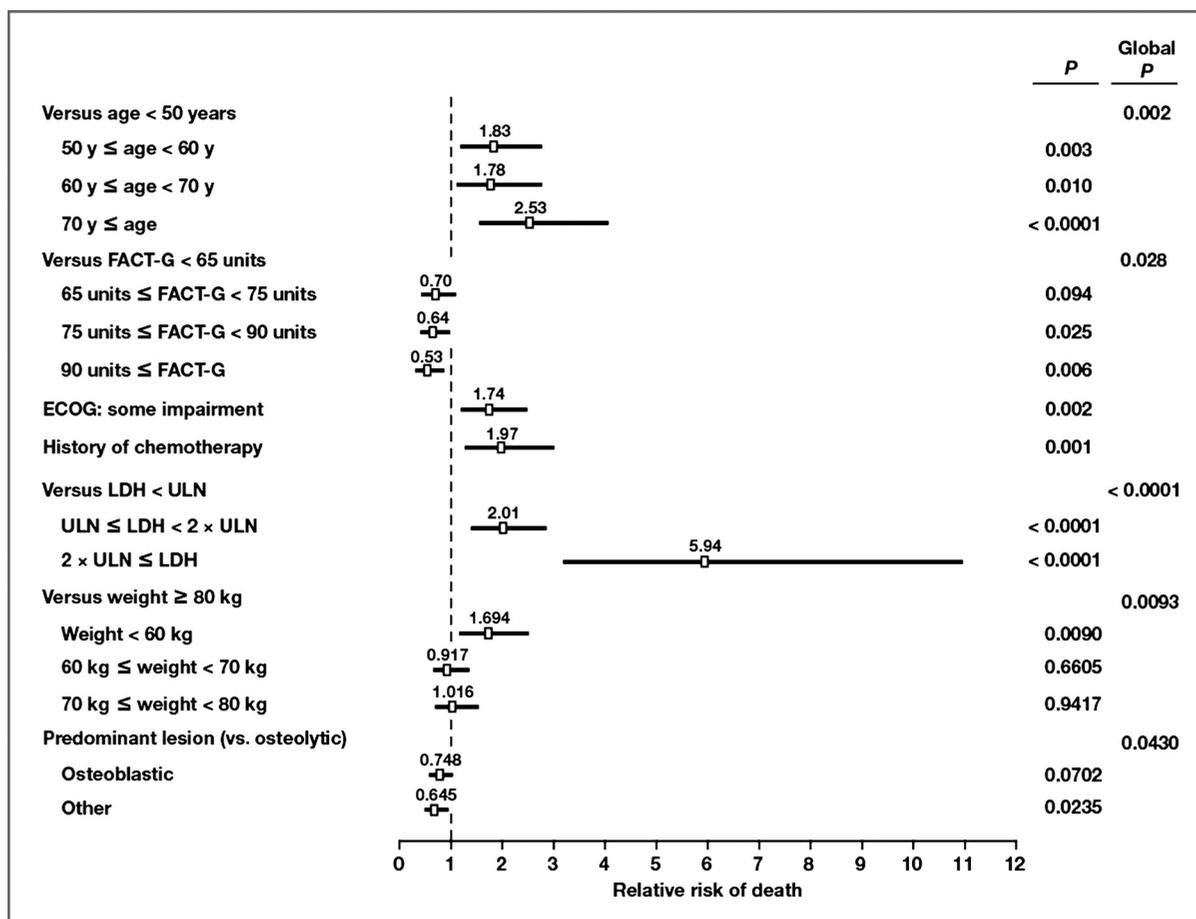
Figure 1. Forest plot of significant prognostic variables in reduced multivariate Cox model for death in patients with bone metastases from breast cancer. Horizontal lines represent the 95% confidence interval. Global *P* values are for all categories versus the reference category and are derived from the full Cox multivariate analysis.

weight < 60 kg, albumin < 35 g/L, FACT-G < 65 units, and SGOT ≥ ULN. Notably, baseline LDH levels were a consistent predictor of mortality throughout the study (e.g., at the 6-, 12-, and 18-month time points).

Discussion

The registration trial comparing ZOL with pamidronate in patients with bone metastases from breast cancer generated an extensive database of demographic characteristics, concomitant therapy, and clinical outcomes, including survival and laboratory parameters that provide a rich data source for exploratory analyses. All patients in the current analysis received ZOL therapy, which remains a standard of care for patients with bone metastases from solid tumors (25). Access to this database has permitted this large, multicenter, multivariate analysis of factors prognostic for survival in patients with bone metastases from breast cancer (30). A key finding from these analyses is the emergence of LDH as a significant and powerful prognostic variable for risk of death in patients with advanced breast cancer.

Other prognostic variables that remained significant in multivariate models included age, ECOG performance status, prior chemotherapy, and FACT-G score. Because these variables have been well recognized as factors prognostic for survival in patients with metastatic breast cancer (14, 31), they provide validation for the methodology used in the current analyses. Univariate and multivariate analyses have identified baseline bone biomarker levels such as NTX and BSAP as prognostic factors for occurrence of SREs in patients with bone metastases (24, 32). However, although both NTX and BSAP were significantly correlated with risk of death in the univariate model in the current analysis, this statistically significant correlation was not maintained for either biomarker in the multivariate model (Table 2).

Notably, LDH is a key enzyme in energy production in many tissues and cell types, and LDH serum concentrations become elevated following tissue injury or during disease states. The potential role of LDH as a prognostic biomarker in oncology has long been recognized. In patients with Ewing's sarcoma of bone ($N = 618$), baseline serum LDH levels were significantly higher in patients with metastatic disease ($P < 0.0001$) and prognostic of shorter disease-free
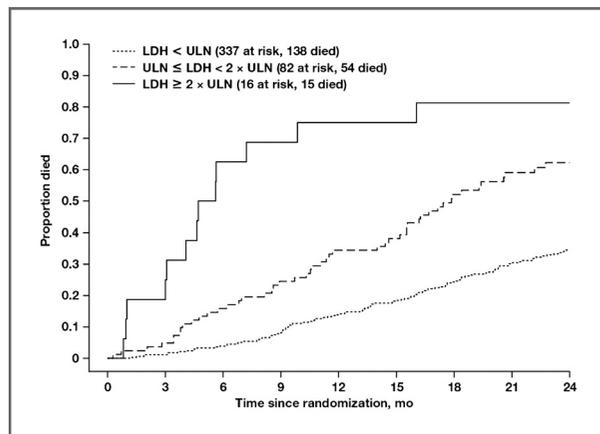
Figure 2. Kaplan–Meier estimates for overall survival of patients with bone metastases from breast cancer treated with ZOL using multivariate modeling by LDH levels.

survival in patients with localized disease versus patients with normal LDH levels ($P < 0.0001$; ref. 33). In small cell lung cancer, serum LDH has been shown to be a significant predictor of survival (29, 34) and is used routinely for assisting treatment decisions using, for example, the Manchester Prognostic Score, which includes serum LDH among a panel of markers (35). In non–small cell lung cancer, analysis of a large database ($N = 2,531$) found that normal baseline LDH levels were predictive of better survival (25). Correlations between baseline LDH levels and survival also have been observed in patients with multiple myeloma, mantle cell lymphoma, and prostate cancer (26–28). Recently, studies in metastatic melanoma have reported that LDH is prognostic for survival (36) and LDH correlated significantly with stage of disease (37). In other recent studies, serum LDH levels were the main prognostic factor for colorectal cancer in a survival prognostic model (38). Moreover, the addition of LDH to the International Myeloma Staging Model was found to improve prognostic value (39). Taken together, these various analyses support the potential prognostic value of baseline LDH levels across several tumor types.

Construction and validation of a practical prognostic index for patients with metastatic breast cancer was reported by Yamamoto and colleagues (40). Multivariate analyses of data from 233 patients with metastatic breast cancer showed that LDH was among 5 factors prognostic for survival. These 5 factors were used to construct a prognostic index that was prospectively evaluated in a validation set of 315 patients with metastatic breast cancer. Notably, a new prognostic score that includes serum LDH measurements has been proposed for patients with brain metastases. This 7-factor prognostic score, which includes serum LDH and HER2 overexpression, successfully predicted survival for a heterogeneous group of 130 patients (41).

A recent study claimed to prospectively validate 2 prognostic scores (combining LDH and either performance status or lymphocyte count) for survival in patients with cancer after first-line chemotherapy (42). All eligible patients ($n = 299$) with metastatic cancer treated at a single center were included, of whom 132 patients had breast cancer (estimated 100–110 with bone metastases). Few previous studies have focused on the prognostic value of LDH in patients with bone metastases. In a retrospective analysis of patients with bone metastases from castration-resistant prostate cancer ($N = 643$), elevated baseline serum LDH levels (>454 U/L) were associated with a nearly 3-fold increased risk of death in the univariate model (RR 2.83; $P < 0.001$), and with a 2-fold increased risk of death in the reduced multivariate model (RR 2.01; $P < 0.001$; ref. 43). Analyses in a smaller group of patients with bone metastases from prostate cancer ($N = 60$) showed that serum LDH level was a significant prognostic indicator for survival both in univariate ($P = 0.0049$) and multivariate ($P = 0.0371$) analyses (44). The current study is believed to be the first to focus on a large cohort of breast cancer patients with bone metastases) in a multicenter setting. Although it is recognized that different isoforms of LDH exist and can be measured separately, a key advantage of total serum LDH as a prognostic indicator is that it is extremely convenient and inexpensive to measure. It is fortunate that total serum LDH in this and other oncology studies is strongly associated with survival, without the need to measure individual isoforms.

The current exploratory analysis used a patient population with bone metastases treated with ZOL, which remains a current standard of care for bone-targeted therapy. However, after the data were collected in this patient population, estrogen receptor and HER2 status in breast cancer came to be routinely measured on tissue blocks. Furthermore, there have been advances in cytotoxic therapy with newer agents such as docetaxel, routine use of aromatase inhibitors as a key component of hormonal therapy, and routine use of targeted therapies such as trastuzumab. In addition, CTCs are in more common use as potential prognostic markers. Although changes inevitably occur during the gathering of data from large studies, the question arises as to whether such changes will affect the prognostic relevance of LDH determined in this study.

Indirect evidence is reassuring in this regard. For example, in a recent study of potential prognostic factors in metastatic prostate cancer ($n = 104$), LDH remained a significant prognostic factor even though newer factors such as HER2 overexpression were included in a multivariate analysis (45). Also, in castration-resistant prostate cancer, a study of the prognostic value of CTCs concluded that the factors most predictive for survival were high LDH concentration and elevated CTC counts ($P < 0.001$, both; ref. 46). In a study of 996 myeloma patients, Terpos and colleagues found that high versus normal LDH had a major impact on OS even when patients have received novel agent-based therapies (median OS 21 versus 51 months, respectively; $P < 0.001$; ref. 39).

We have considered the possible effects of "false positives" that have been reported to occur in assessment of LDH. The effects of any bias introduced by these have been minimized by using categorical LDH values instead of

absolute measurements. Also, the possibility of false positive LDH results would actually reduce the chance of showing an association when one exists. Thus, if false positives were present in the data, the model would more likely yield conservative estimates of the association between LDH and survival.

There are potential limitations in this study worthy of note. Laboratory-specific ULNs for LDH were used to specify cut-off points, in preference to an absolute LDH value as the cutoff. This was considered appropriate to reflect local factors and because some variation in absolute reference ranges was reflected in the ULN across centers. Consequently, it is difficult to directly compare data obtained in this study with those previously reported for patients with advanced cancer with or without bone metastases. If LDH is to be used in the future as a prognostic factor for survival for breast cancer patients with bone metastases, it is desirable to agree on a common way of expressing LDH values across centers. This study had a limited follow-up period and duration of bisphosphonate use, being confined to the duration of the original phase III study. The LDH assessment was recorded at study entry and not at the time of diagnosis of bone metastases (median difference 3.75 months). However, given that the average survival for patients with advanced breast cancer was typically 18 to 26 months after diagnosis of bone metastases, depending on hormonal therapy (23), the limited follow-up is not likely to have any substantial impact on the survival data.

On the basis of the current study, the combination of LDH with other prognostic factors into a weighted prognostic score for survival in patients with bone metastases from breast cancer would be a valuable next step. Such a score would then require confirmation and validation in a future prospective study before adoption into new management guidelines. Assessment of LDH should, therefore, be incorporated into future large breast cancer studies, and LDH also may be an important stratification factor in the design of future randomized trials.

Disclosure of Potential Conflicts of Interest

J. Brown has received honoraria from speakers bureau from Novartis and Amgen and is a consultant and/or advisory board member for Novartis, Amgen, Roche, and Bristol-Myers Squibb. R. Cook is a consultant/advisory board member for Abbott, Amgen, and Novartis. A. Lipton has received commercial research grants from Novartis, Monogram Biosciences, and Oncogene Science; has received honoraria from speakers bureau from Novartis, Amgen, and Genentech; is a consultant/advisory board member for Novartis, Amgen, Galapagos, and Acceleron Pharm; and has given expert testimony for Novartis. R. Coleman has received other commercial support from Novartis; honoraria from speakers bureau from Novartis and Amgen; is a consultant/advisory board member for Novartis and Amgen; and has previously given expert testimony on the behalf of Novartis.

Authors' Contributions

Conception and design: J.E. Brown, A. Lipton, R.E. Coleman
Development of methodology: J.E. Brown, R.J. Cook, A. Lipton
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.E. Brown, R.J. Cook, A. Lipton
Writing, review, and/or revision of the manuscript: J.E. Brown, R.J. Cook, A. Lipton, R.E. Coleman
Study supervision: R.E. Coleman

References

1. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001;27:165–76.
2. Kinnane N. Burden of bone disease. Eur J Oncol Nurs 2007;11 suppl 2: S28–31.
3. Weinfurt KP, Castel LD, Li Y, Timbie JW, Glendenning GA, Schulman KA. Health-related quality of life among patients with breast cancer receiving zoledronic acid or pamidronate disodium for metastatic bone lesions. Med Care 2004;42:164–75.
4. Sutherland CM, Mather FJ. Charity Hospital experience with long-term survival and prognostic factors in patients with breast cancer with localized or regional disease. Ann Surg 1988;207: 569–80.
5. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. J Clin Oncol 2010;28:92–8.
6. Fan C, Oh DS, Wessels L, Weigelt B, Nuyten DS, Nobel AB, et al. Concordance among gene-expression-based predictors for breast cancer. N Engl J Med 2006;355:560–9.
7. U.S. Food and Drug Administration. CellSearch™ Epithelial Cell Kit/CellSpotter™ Analyser - K031588 [cited 2012 16 April]. Available from: http://www.fda.gov/MedicalDevices/ProductsandMedicalProce-

dures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm081239.htm. 2009.
8. Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010;28:5132–9.
9. Diamond JR, Finlayson CA, Borges VF. Hepatic complications of breast cancer. Lancet Oncol 2009;10:615–21.
10. Tampellini M, Berruti A, Gerbino A, Buniva T, Torta M, Gorzegno G, et al. Relationship between CA 15–3 serum levels and disease extent in predicting overall survival of breast cancer patients with newly diagnosed metastatic disease. Br J Cancer 1997;75:698–702.
11. Dunphy FR, Spitzer G, Fornoff JE, Yau JC, Huan SD, Dicke KA, et al. Factors predicting long-term survival for metastatic breast cancer patients treated with high-dose chemotherapy and bone marrow support. Cancer 1994;73:2157–67.
12. Kuru B, Camlibel M, Dinc S, Gulcelik MA, Gonullu D, Alagol H. Prognostic factors for survival in breast cancer patients who developed distant metastasis subsequent to definitive surgery. Singapore Med J 2008;49:904–11.
13. Yavas O, Hayran M, Ozisik Y. Factors affecting survival in breast cancer patients following bone metastasis. Tumori 2007;93:580–6.

14. Coleman RE, Smith P, Rubens RD. Clinical course and prognostic factors following bone recurrence from breast cancer. Br J Cancer 1998;77:336–40.

15. Brown JE, Thomson CS, Ellis SP, Gutcher SA, Purohit OP, Coleman RE. Bone resorption predicts for skeletal complications in metastatic bone disease. Br J Cancer 2003;89:2031–7.

16. Brown JE, Cook RJ, Major P, Lipton A, Saad F, Smith M, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. J Natl Cancer Inst 2005; 97:59–69.

17. Lipton A, Cook R, Saad F, Major P, Garnero P, Terpos E, et al. Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. Cancer 2008;113:193–201.

18. Lipton A, Demers L, Curley E, Chinchilli V, Gaydos L, Hortobagyi G, et al. Markers of bone resorption in patients treated with pamidronate. Eur J Cancer 1998;34:2021–6.

19. Major PP, Cook RJ, Lipton A, Smith MR, Terpos E, Coleman RE. Natural history of malignant bone disease in breast cancer and the use of cumulative mean functions to measure skeletal morbidity. BMC Cancer. 2009;9:272.

20. Kaminski M, Rosen LS, Gordon D, Zheng M, Hei Y-J. Zoledronic acid is superior to pamidronate in patients with breast cancer and multiple myeloma who are at high risk for skeletal complications [poster]. Presented at: Primary Therapy of Early Breast Cancer 9th International Conference; 2005 Jan 26–29; St. Gallen, Switzerland. Abstract 107.

21. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 2001;7:377–87.

22. Rosen LS, Gordon DH, Dugan W Jr, Major P, Eisenberg PD, Provencher L, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 2004;100:36–43.

23. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 2003;98:1735–44.

24. Brown JE, Cook RJ, Lipton A, Costa L, Coleman RE. Prognostic factors for skeletal complications from metastatic bone disease in breast cancer. Breast Cancer Res Treat 2010;123:767–79.

25. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience. J Clin Oncol 1991;9:1618–26.

26. Eleutherakis-Papaiakovou V, Bamias A, Gika D, Simeonidis A, Pouli A, Anagnostopoulos A, et al. Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. Leuk Lymphoma 2007;48:337–41.

27. Hoster E, Dreyling M, Klapper W, Gisselbrecht C, van Hoof A, Kluin-Nelemans HC, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 2008;111:558–65.

28. Smaletz O, Scher HI, Small EJ, Verbel DA, McMillan A, Regan K, et al. Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. J Clin Oncol 2002;20:3972–82.

29. Tas F, Aydiner A, Demir C, Topuz E. Serum lactate dehydrogenase levels at presentation predict outcome of patients with limited-stage small-cell lung cancer. Am J Clin Oncol 2001;24:376–8.

30. Coleman RE, Brown JE, Cook R. Serum lactate dehydrogenase (LDH) is a significant prognostic variable for survival in patients with meta-

static breast cancer: a multivariate analysis [poster]. Presented at: EBCC 6: European Breast Cancer Conference; 2008 Apr 15–19; Berlin, Germany. Abstract nr 468.

31. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. Br J Cancer 1987;55:61–6.

32. Coleman RE, Major P, Lipton A, Brown JE, Lee KA, Smith M, et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. J Clin Oncol 2005;23:4925–35.

33. Bacci G, Ferrari S, Longhi A, Rimondini S, Versari M, Zanone A, et al. Prognostic significance of serum LDH in Ewing's sarcoma of bone. Oncol Rep 1999;6:807–11.

34. Stokkel MP, van Eck-Smit BL, Zwinderman AH, Willems LN, Pauwels EK. Pretreatment serum lactate dehydrogenase as additional staging parameter in patients with small-cell lung carcinoma. J Cancer Res Clin Oncol 1998;124:215–9.

35. Cerny T, Blair V, Anderson H, Bramwell V, Thatcher N. Pretreatment prognostic factors and scoring system in 407 small-cell lung cancer patients. Int J Cancer 1987;39:146–9.

36. Eigentler TK, Figl A, Krex D, Mohr P, Mauch C, Rass K, et al. Number of metastases, serum lactate dehydrogenase level, and type of treatment are prognostic factors in patients with brain metastases of malignant melanoma. Cancer 2011;117:1697–703.

37. Egberts F, Kotthoff EM, Gerdes S, Egberts JH, Weichenthal M, Hauschild A. Comparative study of YKL-40, S-100B and LDH as monitoring tools for Stage IV melanoma. Eur J Cancer 2012;48:695–702.

38. Chibaudel B, Bonnetain F, Shi Q, Buyse M, Tournigand C, Sargent DJ, et al. Alternative end points to evaluate a therapeutic strategy in advanced colorectal cancer: evaluation of progression-free survival, duration of disease control, and time to failure of strategy—an Aide et Recherche en Cancerologie Digestive Group Study. J Clin Oncol 2011;29:4199–204.

39. Terpos E, Katodritou E, Roussou M, Pouli A, Michalis E, Delimpasi S, et al. High serum lactate dehydrogenase adds prognostic value to the international myeloma staging system even in the era of novel agents. Eur J Haematol 2010;85:114–9.

40. Yamamoto N, Watanabe T, Katsumata N, Omuro Y, Ando M, Fukuda H, et al. Construction and validation of a practical prognostic index for patients with metastatic breast cancer. J Clin Oncol 1998;16:2401–8.

41. Le Scodan R, Massard C, Jouanneau L, Coussy F, Gutierrez M, Kirova Y, et al. Brain metastases from breast cancer: proposition of new prognostic score including molecular subtypes and treatment. J Neurooncol 2012;106:169–76.

42. Tredan O, Ray-Coquard I, Chvetzoff G, Rebattu P, Bajard A, Chabaud S, et al. Validation of prognostic scores for survival in cancer patients beyond first-line therapy. BMC Cancer 2011;11:95.

43. Cook RJ, Coleman R, Brown J, Lipton A, Major P, Hei YJ, et al. Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. Clin Cancer Res 2006;12:3361–7.

44. Naruse K, Yamada Y, Aoki S, Taki T, Nakamura K, Tobiume M, et al. Lactate dehydrogenase is a prognostic indicator for prostate cancer patients with bone metastasis. Hinyokika Kiyo 2007;53: 287–92.

45. Yamada Y, Nakamura K, Aoki S, Tobiume M, Zennami K, Kato Y, et al. Lactate dehydrogenase, Gleason score and HER-2 overexpression are significant prognostic factors for M1b prostate cancer. Oncol Rep 2011;25:937–44.

46. Scher HI, Jia X, de Bono JS, Fleisher M, Pienta KJ, Raghavan D, et al. Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. Lancet Oncol 2009;10:233–9.

Clinical Cancer Research

Serum Lactate Dehydrogenase Is Prognostic for Survival in Patients with Bone Metastases from Breast Cancer: A Retrospective Analysis in Bisphosphonate-Treated Patients

Janet E. Brown, Richard J. Cook, Allan Lipton, et al.

Updated version	Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-12-1397

Cited articles	This article cites 43 articles, 9 of which you can access for free at: http://clincancerres.aacrjournals.org/content/18/22/6348.full#ref-list-1

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/18/22/6348. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.