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Clinical benefit in patients with metastatic bone disease: results of a phase 3 study of denosumab versus zoledronic acid[†]

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Background: Patients with metastatic bone disease are living longer in the metastatic stage due to improvements in cancer therapy, making strategies to prevent the aggravation of bone disease and its complications, such as skeletal-related events (SREs) and pain, increasingly important.

Patients and results: In this phase 3 trial in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma, denosumab reduced the risk of radiation to bone by 22% relative to zoledronic acid ($P = 0.026$), prevented worsening of pain and pain interference (2-point increase in Brief Pain Inventory score; $P < 0.05$ versus zoledronic acid), and reduced the frequency of a shift from no/weak opioid analgesic use to strong opioids ($P < 0.05$)

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versus zoledronic acid at months 3–5). Denosumab delayed the time to moderate-to-severe pain compared with zoledronic acid in patients with mild or no pain at the baseline ($P = 0.04$), supporting early treatment. Health-related quality-of-life scores were similar in both groups. The number needed to treat to avoid one SRE for denosumab was 3 patient-years versus placebo and 10 patient-years versus zoledronic acid.

Conclusion: The use of denosumab was associated with better prevention of the complications of metastatic bone disease secondary to solid tumors or multiple myeloma versus zoledronic acid.

Key words: bone pain, denosumab, metastatic bone disease, quality of life, skeletal-related events, zoledronic acid

introduction

Advanced cancer is frequently associated with bone metastases, often leading to skeletal-related events (SREs) including pathologic fracture, radiation to bone, surgery to bone, and spinal cord compression [1]. SREs are potentially devastating complications that can increase morbidity, cause debilitating pain, and impair mobility. The burden of metastatic bone disease on patients is well documented [1–3]. In particular, pain in patients with bone metastases can be severe, progressive, and burdensome, requiring palliation with analgesics; such pain is frequently intractable, even to opioid therapy [4–8]. Opioid medications are associated with gastrointestinal, neurologic, and respiratory effects [9], which may cause physicians and patients to resist these medications [10, 11].

Due to improvements in cancer therapies for solid tumors and multiple myeloma, patients are now living longer with metastatic disease. This has resulted in a paradigm shift wherein the management of metastatic bone disease is of increasing relevance because of the need to preserve the quality of life for an extended period. Thus, with the management of cancer as a chronic disease, strategies to prevent aggravation of bone disease offer the opportunity to improve patients' lives through the reduction in SREs and delayed worsening of skeletal pain. Early intervention may provide additional benefits as evidenced by the results of a study in patients with metastatic lung cancer which showed that early palliative care enhanced the quality of life and reduced the aggressive end-of-life care [12].

The management of metastatic bone disease can be achieved through an approach integrating the use of analgesics, radiation or surgery to bone, chemotherapy, and bone-targeted agents to prevent SREs [13]. The bisphosphonate zoledronic acid (Zometa®) is frequently used to prevent SREs in patients with advanced cancer and bone metastasis [14–18]. Zoledronic acid has been shown to reduce pain in patients with breast cancer and bone metastases [19] and attenuate pain worsening in patients with prostate cancer and bone metastases [20].

Denosumab (XGEVA®) is a fully human monoclonal antibody with high affinity and specificity for human RANKL recently approved for the prevention of SREs in patients with solid tumors [21]. Metastatic tumor cells in the bone secrete cytokines that increase RANKL expression, resulting in the activation of osteoclast-mediated bone destruction [22]. By inhibiting RANKL, denosumab prevents osteoclast-mediated bone destruction and decreases the complications of bone metastases in patients with advanced cancer [23–26].

In a phase 3 trial in patients with solid tumors (excluding breast and prostate cancer) and multiple myeloma, denosumab

was non-inferior to zoledronic acid for the prevention or delay of SREs [7]. Here, we report additional end points from this phase 3 trial, including the number needed to treat (NNT), as well as patient-reported outcomes of pain and health-related quality of life (HRQoL).

methods

study design

This was an international, randomized, double-blind, double-dummy phase 3 trial comparing the efficacy and safety of subcutaneous denosumab (120 mg) administered Q4W versus intravenous zoledronic acid (4 mg, dose adjusted for renal function) given Q4W for the treatment of established bone metastases [7]. Patients were equally allocated (1:1) to one of the two treatment arms using a computer-generated randomization schedule with a permuted block size of 4. Randomization was stratified by tumor type (non-small cell lung cancer or multiple myeloma or other), previous SRE (yes or no), and systemic anti-cancer therapy (yes or no). The study was approved by the investigational review board or ethics committee at each site. Patients provided informed consent before any study procedures. Daily calcium and Vitamin D supplements were strongly recommended. The duration of the trial was event-driven and the primary analysis was to be conducted after ~745 patients had experienced an SRE.

patients

Eligible patients were ≥ 18 years old diagnosed with solid tumors (except for breast and prostate cancer) or multiple myeloma with radiographic evidence of ≥ 1 bone metastasis or bone disease and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, adequate organ function, and a life expectancy of ≥ 6 months. Exclusion criteria included creatinine clearance < 30 mL/min, prior i.v. bisphosphonate use or use of oral bisphosphonates for the treatment of bone metastases, a history of osteonecrosis/osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed oral/dental surgery, or planned invasive dental procedure. Prior oral bisphosphonate use for the treatment of other conditions (e.g. osteoporosis) was allowed.

outcome measures

Radiographic evaluation was conducted every 12 weeks; additional radiographic assessments were carried out as needed. Fractures and spinal cord compression were confirmed through blinded central imaging review. An analgesia quantification algorithm was employed to compute a score for analgesic use (Table 1). Patient-reported outcomes were collected at the baseline and every 4 weeks thereafter and included pain severity and interference as measured by the Brief Pain Inventory (BPI)-Short Form [27] and HRQoL as measured by the Functional Assessment of Cancer Therapy-General instrument (FACT-G).

Table 1. Analgesic score

Score	Definition
0	No analgesic use
1	Non-opioid analgesics (e.g. NSAIDs)
2	Weak opioid analgesics (e.g. meperidine, codeine, tramadol)
3	Strong opioids, ≤ 75 oral morphine-equivalents (OME) per day
4	Strong opioids, >75 –150 OME per day
5	Strong opioids, >150 –300 OME per day
6	Strong opioids, >300 –600 OME per day
7	Strong opioids, >600 OME per day

end points

The primary efficacy and safety outcomes of this study have been reported previously [7]. The prespecified end points included in the present report are: time to first on-study SRE or hypercalcemia of malignancy (a serum calcium value, albumin-adjusted if necessary, of CTCAE v3.0 grades 2 or 3 [>11.5 mg/dl (>2.9 mmol/l)]; ionized calcium >1.5 mmol/l]; time to first radiation to bone; the skeletal morbidity rate (SMR), defined as the number of occurrences of any SRE for a subject, allowing one event per assessment period (21 days), divided by that patient's time at risk; analgesic use; pain severity and pain interference with activity, affect, and overall; and FACT-G scores. Additional end points include: the proportion of patients who experienced more than one SRE while on study; and the NNT for the first on-study SRE and first and subsequent on-study SREs. Based on the event-driven nature of the trial, the NNT for denosumab compared with zoledronic acid was calculated as the inverse of the difference in the annualized or patient-year adjusted rates between two treatments: $NNT = 1/[(\text{number of zoledronic acid SREs/patient-years}) - (\text{number of denosumab SREs/patient-years})]$. The NNT for denosumab versus placebo for first on-study SRE was calculated using placebo group data from a registrational trial of zoledronic acid [28].

statistical analyses

For time-to-event end points, the Kaplan–Meier estimates were generated and the hazard ratio (HR) of denosumab versus zoledronic acid and the two-sided 95% confidence interval (CI) were estimated using a Cox proportional hazards model stratified by the randomization stratification factors. The SMR was compared between treatment groups using the Cochran–Mantel–Haenszel test stratified by the randomization stratification factors. The responder analyses for HRQoL (FACT-G), analgesic use, pain, and pain interference and the proportions of patients who met each responder criterion were summarized by visit up to the visit where $\geq 50\%$ of the patients had withdrawn due to death, disease progression, or withdrawal of consent. The χ^2 test was used to compare proportions between the treatment groups. No multiplicity adjustments were made.

The authors had access to the relevant study data and participated in the drafting, reviewing, and critical revision of this paper. The decision to submit the manuscript was at the discretion of the authors.

results

patients and disposition

A total of 1776 patients were randomized (denosumab, $n = 886$ and zoledronic acid, $n = 890$) from 33 countries: 55% of the patients were enrolled in Europe, 23% in North America, 16% in Latin America, and 7% in other regions. Eighty percent of the study population discontinued before the primary analysis

Table 2. Baseline pain, health-related quality of life (HRQoL), and analgesic use

Characteristics	Zoledronic acid ($N = 890$)	Denosumab ($N = 886$)
Pain, n (%)		
No (0)	85 (10)	86 (10)
Mild (1–4)	232 (26)	275 (31)
Moderate (5–6)	205 (23)	193 (22)
Severe (7–10)	308 (35)	271 (31)
HRQoL, mean (SD)		
FACT-G total score ^a	68.9 (15.8)	68.2 (16.1)
Physical well-being subscale score	16.9 (5.9)	16.6 (6.3)
Functional well-being subscale score	14.3 (5.9)	14.4 (6.0)
Analgesic use, n (%)	570 (64)	583 (66)
Analgesic score		
Median (range)	2 (0, 7)	2 (0, 7)
Analgesic score, n (%)		
0	320 (36.0)	303 (34.2)
1	114 (12.8)	122 (13.8)
2	125 (14.0)	134 (15.1)
3	154 (17.3)	158 (17.8)
4	65 (7.3)	52 (5.9)
5	48 (5.4)	44 (5.0)
6	36 (4.0)	42 (4.7)
7	28 (3.1)	31 (3.5)

^aRange for FACT-G overall: 0–108; range for FACT-G subscales: 0–28.

cut-off date; the primary reasons for discontinuation included death, withdrawal of consent, and disease progression [7].

Baseline demographics and disease characteristics for this study have been reported [7] and were balanced between the treatment groups. Briefly, of the enrolled patients, most were men (64%), the mean (SD) age was 60 (11) years, and 40% had a primary malignancy of non-small cell lung cancer. Baseline pain, HRQoL, and analgesic use are reported in Table 2 and were also balanced between treatment groups. Approximately 41% of the denosumab group and 36% of the zoledronic acid group had no or mild pain at the baseline (BPI worst pain score 0–4). The majority of patients were on analgesic medication (66% denosumab and 64% zoledronic acid), with 36% and 37%, respectively, receiving strong opioid medication.

efficacy

effects on SREs

Denosumab significantly delayed the time to first SRE or hypercalcemia of malignancy [Figure 1; Kaplan–Meier estimate, median 19.0 months for denosumab versus 14.4 months for zoledronic acid; HR 0.83 (95% CI 0.71–0.97); $P = 0.022$]. Denosumab also significantly reduced the risk of radiation to bone by 22% [Figure 2; HR 0.78 (95% CI 0.63–0.97); $P = 0.026$; median time to radiation was not estimable for either treatment group]. Fewer patients experienced one or more SREs with denosumab versus zoledronic acid: 31.4% versus 36.3% (13.5% relative reduction). There was a 17.3%

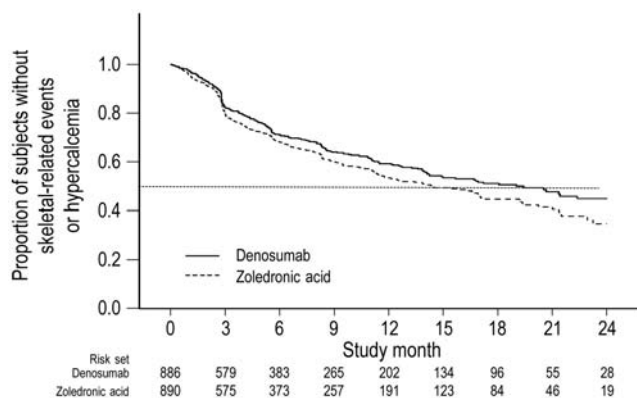


Figure 1 Time to first on-study SRE or hypercalcemia of malignancy.

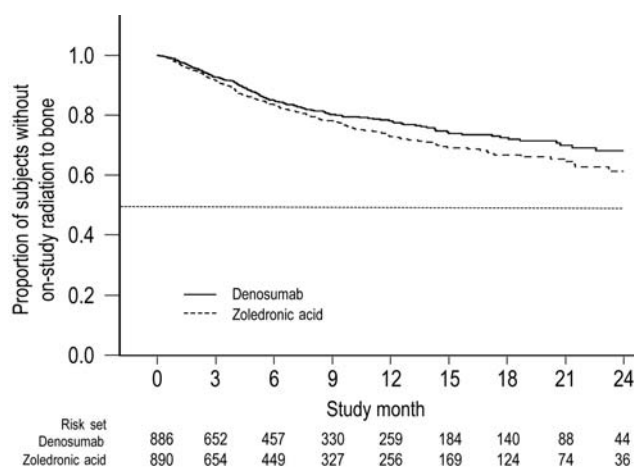


Figure 2 Time to first on-study radiation to bone.

relative reduction in the SMR for denosumab versus zoledronic acid (0.86 versus 1.04; $P = 0.053$).

For the end point of time to first SRE, the NNT with denosumab versus zoledronic acid was 9.9 patient-years, indicating that 9.9 patients treated for 1 year with denosumab instead of zoledronic acid would result in the prevention of one first SRE. For the end point of time to first and subsequent SREs, the NNT with denosumab versus zoledronic acid was 10.4 patient-years, indicating that 10.4 patients treated with denosumab instead of zoledronic acid for 1 year would result in the prevention of one first or subsequent SRE. The NNT for denosumab versus placebo was 3.0 patient-years.

patient-reported outcomes

pain

The smallest change that a patient would find meaningful (minimally important difference) for the BPI worst pain rating is generally considered to be a change of 2 points [29]. Denosumab reduced the risk of a 2-point increase (i.e. worsening) in the worst pain score by 15% relative to zoledronic acid (median time to 2-point increase: 5.6 months for denosumab versus 4.7 months for zoledronic acid; $P = 0.02$) (Supplementary Figure S1A, available at *Annals of Oncology* online). For the time to moderate/severe pain (worst pain score

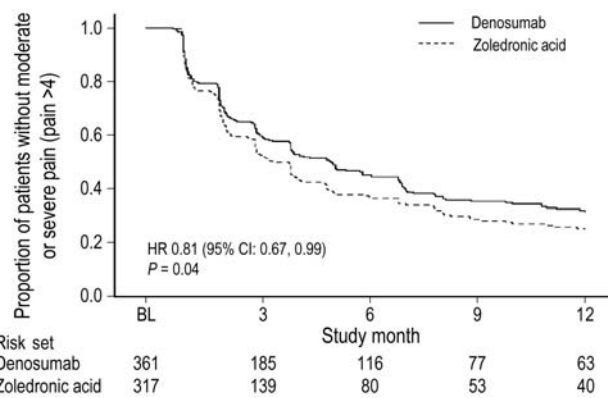


Figure 3 Pain worsening: time to moderate or severe pain among patients with no or mild pain at the baseline.

>4 points), there was a trend in the delay in pain progression with denosumab (1.9 months for denosumab versus 1.2 months for zoledronic acid; risk reduction of 9%; $P = 0.11$) (Supplementary Figure S1B, available at *Annals of Oncology* online). In the subset of patients with no or mild pain at the baseline, denosumab significantly delayed the time to moderate-to-severe pain relative to zoledronic acid (4.7 months for denosumab versus 3.4 months for zoledronic acid; risk reduction of 19%; $P = 0.04$) (Figure 3).

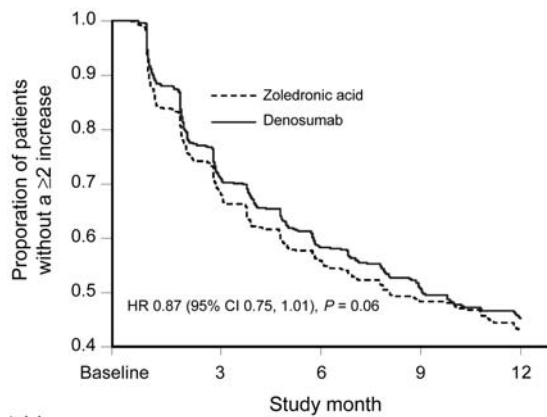
The median time to a 2-point decrease (i.e. improvement) in the worst pain score was 2.8 months for both treatment groups ($P = 0.87$).

pain interference

The interference of pain with other aspects of life including activity, affect (mood), and overall (a composite end point including activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life) was evaluated as part of the BPI. For interference with ‘activity’, there was some evidence of delay in the time to increased pain interference (i.e. ≥ 2 point increase from the baseline) for denosumab relative to zoledronic acid (6.5 months for denosumab versus 5.8 months for zoledronic acid; $P = 0.08$). For interference with ‘affect’, denosumab significantly delayed the time to increased pain interference relative to zoledronic acid (7.2 months for denosumab versus 5.8 months for zoledronic acid; $P = 0.04$). There was also evidence of delay for the time to overall increased pain interference with denosumab relative to zoledronic acid (8.6 months for denosumab versus 7.7 months for zoledronic acid; $P = 0.06$) (Figure 4).

health-related quality of life

Overall, the mean FACT-G scores increased slightly over time and were similar between treatment groups with no notable differences in FACT-G scores observed between the treatment groups during the study. Similarly, the mean scores for the FACT-G physical well-being and functional well-being subscales increased slightly over time; no differences were observed between the treatment groups. These results suggest that both treatments were associated with the maintenance of HRQoL in these patients.



Patients at risk:					
Zoledronic acid	772	415	275	196	157
Denosumab	768	427	283	205	160

Figure 4 Worsening of pain interference.

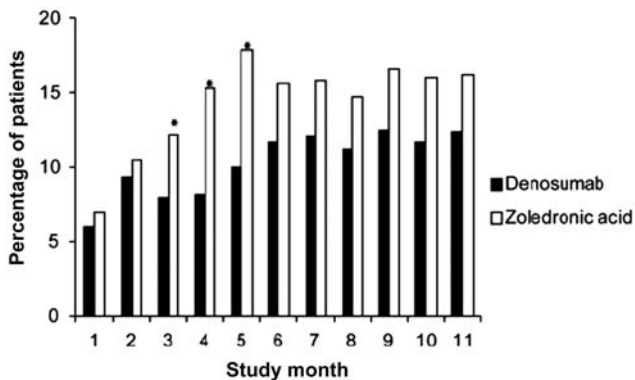


Figure 5 Proportion of patients with no or low analgesic use (AQA score ≤ 2) at the baseline who shifted to strong opioid analgesics (AQA score ≥ 3). Denosumab, $n = 559$; zoledronic acid, $n = 559$. $P < 0.03$ at month 3 and $P = 0.001$ at months 4 and 5.

analgesic use

The mean AQA scores were stable over the course of the study and were similar between treatment groups. A shift to strong opioid use typically represents clinician and patient awareness of a clinically meaningful worsening of a patient's pain. In patients with an analgesic score of ≤ 2 (no or weak opioid use) at the baseline, at all time points, fewer patients in the denosumab group than in the zoledronic acid group shifted to strong opioid analgesic use (score ≥ 3 ; e.g. buprenorphine, fentanyl, hydromorphone, morphine, or oxycodone) (Figure 5). The difference between the treatment groups was statistically significant at months 3, 4, and 5. On average over the 11 months, there was a 27% relative increase in the proportion of zoledronic acid-treated patients who shifted to strong opioid analgesics compared with denosumab-treated patients.

discussion

In this phase 3 trial of bone-targeted agents in patients with advanced solid tumors (excluding breast and prostate cancer)

or multiple myeloma, denosumab was significantly more effective than zoledronic acid for SRE-related end points and substantially delayed pain progression and worsening of pain interference. Denosumab not only delayed skeletal complications as previously demonstrated [7], but also significantly delayed the time to first SRE or hypercalcemia of malignancy, a potentially life-threatening condition associated with advanced bone metastases. Radiation to bone is an essential tool in the management of patients with metastatic bone disease and is frequently used to control pain and treat pathological fractures or spinal cord compression. Here, we show that denosumab was more effective than zoledronic acid in preventing radiation to bone.

Skeletal pain is one of the most burdensome and difficult to treat aspects of metastatic bone disease. Reflective of clinical practice, in this study, not all of the patients with moderate-to-severe pain received opioid analgesics, perhaps because of physician avoidance due to concerns about adverse effects (cognitive impairment, nausea, and constipation) or because of patient resistance based on fears of dependency, adverse effects, or exhaustion of all palliative options [11]. Despite the inclusion of over 50 different tumor types in the study, a difference in pain, pain interference, and analgesic use was noted between treatment groups. Relative to zoledronic acid, denosumab significantly delayed the worsening of pain and pain interference as measured by the BPI. The difference between the treatment groups for the delay of moderate or severe pain was most pronounced in patients who had no or mild pain at the baseline, indicating decreased pain progression for the denosumab group relative to the zoledronic acid group. Similarly, for the shift to higher analgesic use, statistically significant differences between the groups were observed at months 3, 4, and 5 in patients with no/mild analgesic use at the baseline. The finding that early intervention with denosumab versus zoledronic acid prevented pain progression and led to decreased analgesic use in patients with bone metastases with no or mild pain at the baseline indicates that skeletal protection through osteoclast inhibition may play an important role in pain prevention.

Despite the differences between the groups for the delay of pain and pain interference worsening, no differences between denosumab and zoledronic acid were observed for the overall quality of life. At the time this study commenced, the FACT bone pain subscale had not yet been developed. Therefore, as the FACT-G is not specific for advanced cancer patients with bone metastases, the ability to distinguish the effects of SREs and cancer-related bone pain on the quality of life may be limited. In addition, the timing of the FACT-G assessments may not have aligned with the timing of experiencing SREs or pain, thus limiting the opportunity to observe treatment differences [30].

NNT analyses are used to describe the relative benefit of a treatment. The determination of NNT based on patient-year exposure is most appropriate for event-driven trials such as this one where patients may be on the trial for varying amounts of time. For the present trial, NNT analysis showed that the treatment of ~ 10 patients for 1 year with denosumab instead of zoledronic acid would prevent one SRE. The NNT for denosumab versus placebo was 3, showing that the treatment

of as few as three patients for 1 year with denosumab would prevent one SRE. For comparison, an NNT analysis of trials evaluating radioisotopes versus placebo in patients with metastatic bone pain produced an NNT of 5 [31]. The indirect treatment effect of denosumab versus placebo was established under constancy assumption that the effect size of zoledronic acid versus placebo in the current trial would remain the same as that in the historical registrational trial of zoledronic acid [28]. The current trial was designed and carried out with the intent to keep all important design and conduct features from the historical trial that might influence the effect size of zoledronic acid, but some differences were unavoidable and the constancy assumption could be challenging to verify. Importantly, the present comparison, which is between two active treatments rather than between treatment and placebo, shows that the additional benefit of using denosumab over zoledronic acid can be realized through the treatment of a relatively small number of patients.

The observed combination of decreased risk of radiation to bone and prevention of pain worsening and pain interference with functioning in patients treated with denosumab relative to zoledronic acid indicates a positive contribution of early skeletal management in patients with bone metastases. Taken together, these results provide a body of evidence for the benefit of denosumab relative to zoledronic acid in patients with metastatic bone disease.

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disclosures

SVR has received funding for clinical trials and honoraria for advisory roles for Amgen. RM has participated on advisory boards for Amgen, Novartis, and Roche and has received speaker honoraria from Amgen and Roche. DLP FG and CSC have served as consultants to Amgen. DHH has received research funding and served on a speaker bureau for Amgen. YQ AF KC and HY are employees of Amgen and own stock/stock options in Amgen. HY also reports research funding from Amgen. All remaining authors have declared no conflicts of interest.

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Clinicopathological analysis of GATA3-positive breast cancers with special reference to response to neoadjuvant chemotherapy

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Background: The aim of this study was to investigate the clinicopathological characteristics of GATA binding protein 3 (GATA3)-positive breast cancers as well as the association of GATA3 expression with response to chemotherapy.

Patients and methods: Tumor specimens obtained before neoadjuvant chemotherapy [paclitaxel followed by 5-fluorouracil/epirubicin/cyclophosphamide] from breast cancer patients ($n = 130$) were subjected to immunohistochemical and mutational analysis of GATA3 and DNA microarray gene expression analysis for intrinsic subtyping.

Results: Seventy-four tumors (57%) were immunohistochemically positive for GATA3. GATA3-positive tumors were significantly more likely to be lobular cancer, estrogen receptor (ER)-positive, progesterone receptor (PgR)-positive, Ki67-negative, and luminal A tumors. Somatic mutations were found in only three tumors. Pathological complete response (pCR) was observed in 8 (11%) GATA3-positive tumors and in 22 (39%) GATA3-negative tumors. Multivariate analysis showed that tumor size, human epidermal growth factor receptor 2 (HER2), and GATA3 were independent predictors of pCR.

Conclusions: GATA3-positive breast cancers showed luminal differentiation characterized by high ER expression and were mostly classified as luminal-type tumors following intrinsic subtyping. Interestingly, GATA3 was an independent predictor of response to chemotherapy, suggesting that GATA3 might be clinically useful as a predictor of a poor response to chemotherapy.

Key words: breast cancer, GATA3, intrinsic subtype, microarray, neoadjuvant chemotherapy, pathological complete response

introduction

GATA binding protein 3 (GATA3) belongs to the GATA family, which consists of six GATA transcription factors (GATA1–6) that bind to the consensus (A/T)GATA(A/G)

motif [1]. GATA3 is a 444-amino-acid transcription factor located in 10p15 and possesses an activation domain (exons 2 and 3) and a DNA binding domain (exons 4 and 5) [2]. GATA3 was initially identified as a DNA-binding protein involved in the activation of transcription at the T-cell receptor alpha locus and has been shown to be implicated in the development of T-cells. Later studies have revealed that GATA3 is also involved in the development of various organs including the mammary gland [1].

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