American Society of Clinical Oncology Executive Summary of the Clinical Practice Guideline Update on the Role of Bone-Modifying Agents in Metastatic Breast Cancer


ABSTRACT

To update the recommendations on the role of bone-modifying agents in the prevention and treatment of skeletal-related events (SREs) for patients with metastatic breast cancer with bone metastases.

Methods

A literature search using MEDLINE and the Cochrane Collaboration Library identified relevant studies published between January 2003 and November 2010. The primary outcomes of interest were SREs and time to SRE. Secondary outcomes included adverse events and pain. An Update Committee reviewed the literature and re-evaluated previous recommendations.

Results

Recommendations were modified to include a new agent. A recommendation regarding osteonecrosis of the jaw was added.

Recommendations

Bone-modifying agent therapy is only recommended for patients with breast cancer with evidence of bone metastases; denosumab 120 mg subcutaneously every 4 weeks, intravenous pamidronate 90 mg over no less than 2 hours, or zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks is recommended. There is insufficient evidence to demonstrate greater efficacy of one bone-modifying agent over another. In patients with a calculated serum creatinine clearance of more than 60 mg/min, no change in dosage, infusion time, or interval of bisphosphonate administration is required. Serum creatinine should be monitored before each dose. All patients should receive a dental examination and appropriate preventive dentistry before bone-modifying agent therapy and maintain optimal oral health. Current standards of care for cancer bone pain management should be applied at the onset of pain, in concert with the initiation of bone-modifying agent therapy. The use of biochemical markers to monitor bone-modifying agent use is not recommended.

INTRODUCTION

The American Society of Clinical Oncology (ASCO) first published evidence-based clinical practice guidelines for use of bisphosphonates in breast cancer in 2000. ASCO previously updated these guidelines on bisphosphonates in breast cancer in 2003. Reflecting the Update Committee’s recognition of new types of agents, including osteoclast inhibitors such as denosumab, and others that may be available for future updates of this guideline, this guideline uses the term bone-modifying agents.

As a result of changes in the field, the scope of this guideline has been narrowed to the use of bone-modifying agents for patients with metastatic breast cancer. A separate update will cover the role of bone-modifying agents as adjuvant treatment of breast cancer and in managing treatment-associated bone loss. Please note that the term bisphosphonate in specific recommendations used in 2003 (Recommendations 1, 2, 4, 6, and 7) has been changed to the term bone-modifying agent.

Update Type

This guideline is an update. This type of update is one in which a systematic review found some new evidence and, consequently, some recommendations were changed or added. The majority of the recommendations are the same as in the 2003 guidelines for metastatic breast cancer. No additional data are available with regard to the dose, dose interval, or duration of therapy of bone-modifying agents. The
current guideline has added a recommendation regarding osteonecrosis of the jaw (ONJ), a condition recognized after the development of the 2003 guidelines. This guideline on metastatic breast cancer also reviews data on a new bone-modifying agent, denosumab. However, the US Food and Drug Administration (FDA) has not approved ibandronate for use in patients with breast cancer metastatic to the bone at the time of publication. For each of the recommendations, clinical judgment should also take into consideration the patient’s general performance status, patient preferences, and overall prognosis.

**METHODOLOGY**

This guideline was reviewed and approved by the *Journal of Clinical Oncology* and the ASCO Clinical Practice Guidelines Committee and the Board of Directors.

**Literature Search Strategy**

For this guideline, computerized literature searches of MEDLINE and the Cochrane Collaboration Library were conducted. Searches of the English-language literature from January 2003 to July 15, 2009, were conducted to address each of the original guideline questions; subsequently, additional searches on adverse events were conducted. An additional search for randomized controlled trials (RCTs) reporting efficacy and case-control or cohort studies on adverse events published between July 2009 and November 2010 was conducted. Specific numbers of studies found in the literature search, the literature search terms, and a QUORUM diagram are available online in the guideline and Data Supplements 4 and 5 at www.asco.org/guidelines/bisphosbreast.

**Inclusion/Exclusion Criteria**

Articles were selected for inclusion if they met the following criteria: participants had metastatic breast cancer and were randomly assigned to receive a bone-modifying agent or placebo or an alternative intervention. Outcome measures for efficacy and adverse event studies included at least one of the following: skeletal-related events (SREs) and time to SRE, adverse events, pain, and quality of life (see Definition of Terms). Searches for efficacy outcomes were limited to published phase III RCTs, systematic reviews, and meta-analyses. For adverse events, the search was broadened to include case-control and cohort studies.

**THE BOTTOM LINE**

**ASCO GUIDELINE UPDATE**

**The Role of Bone-Modifying Agents (BMAs) in Metastatic Breast Cancer**

**Intervention**

- Bone-modifying agents (BMAs), including bisphosphonates

**Target Audience**

- Medical Oncologists, Radiation Oncologists, Surgical Oncologists, Palliative Care Providers

**Key Recommendations**

- BMAs are recommended for patients with metastatic breast cancer with evidence of bone destruction.
- Denosumab 120 mg subcutaneously every 4 weeks; intravenous (IV) pamidronate 90 mg over no less than 2 hours every 3 to 4 weeks; or IV zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks
- One BMA is not recommended over another.
- In patients with creatinine clearance $\geq 60$ mL/min, no change in dosage, infusion time, or interval is required; monitor creatinine level with each intravenous bisphosphonate dose.
- In patients with creatinine clearance $< 30$ mL/min or on dialysis who may be treated with denosumab, close monitoring for hypocalcemia is recommended.
- All patients should have a dental examination and preventive dentistry before using a BMA.
- At onset of cancer bone pain, provide standard of care for pain management and start BMAs.
- Use of biochemical markers to monitor BMA use is not recommended for routine care.

**Methods**

- Systematic review of medical literature and analysis of the medical literature by the Update Committee of an Expert Panel

**Additional Information**

- The recommendations, clinical questions, and a brief summary of the literature and discussion are in this Executive Summary.

The full guideline, with comprehensive discussions of the literature, methodology, full reference list, evidence tables, and clinical tools and resources, can be found at www.asco.org/guidelines/bisphosbreast.
Results on denosumab (two phase II trials modifying agent. The studies reviewed for this guideline were phase II changed from 2003 because of the results of trials of a new bone-modifying agent. The definition may or may not include hypercalcemia of malignancy.

Skeletal morbidity period rate is the number of 12-week periods with new skeletal complications, divided by the total observational time. Skeletal morbidity rate is the number of SREs per year. Multievent analysis is an analysis of data on all clinically relevant SREs and time to each event.

Guideline Policy
This Executive Summary for physicians is an abridged summary of an ASCO® practice guideline. The practice guideline and this summary are not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This summary does not recommend any particular product or course of medical treatment. Use of the practice guideline and this summary is voluntary. The full practice guideline and additional information are available at www.asco.org/guidelines/bisphosbreast.

Guidelines and Conflict of Interest
The Update Committee was assembled in accordance with ASCO’s Conflict of Interest Management Procedures for Clinical Practice Guidelines ("Procedures," summarized at www.asco.org/guidelines/coi). Members of the Update Committee completed ASCO’s disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Committee did not disclose any such relationships.

Table 1 lists the recommendations from the 2003 guideline and the 2011 guideline update.

Clinical Question 1
What are the indications for using bone-modifying agents to reduce the risk of SREs in patients with metastatic breast cancer? When is the best time to initiate treatment with bone-modifying agents?

Literature update and discussion. This recommendation was changed from 2003 because of the results of trials of a new bone-modifying agent. The studies reviewed for this guideline were phase II trials, phase III trials, and follow-up studies of phase III clinical trial results on denosumab (two phase II trials2,3 and one phase III trial4), ibandronate (two phase III trials/analyses of oral ibandronate5,6 and two phase III trials of intravenous [IV] ibandronate7,8), pamidronate (in the follow-up studies of the phase III zoledronic acid trial9,10 and as a comparator in two phase II trials2,3), and zoledronic acid (two follow-up studies of a phase III trial9,10 and two new RCTs11,12). These trials found that all four agents reduce SREs, the time to SRE, and skeletal morbidity period rate. Both the IV and oral formulations of ibandronate are approved for use in this setting in some countries outside the United States.

The guideline reviews data on a new agent, denosumab, a fully human monoclonal antibody to receptor activator of nuclear factor-κ-β ligand. Because ibandronate is not approved by the FDA, the recommendation did not change to specify its use. There are no new reports on clodronate in the metastatic bone disease setting.

Clinical Question 2
What is the role of bone-modifying agents in the presence of extraskeletal metastases without evidence of bone metastases?

Literature update and discussion. This recommendation remains unchanged from 2003. There have been no new clinical trials reported with patients with breast cancer with extraskeletal metastases but who do not have evidence of bone metastases.

Clinical Question 3A
What are the renal safety concerns of bone-modifying agent therapy?

Literature update and discussion. Pamidronate and zoledronic acid are associated with renal deterioration, particularly in patients with pre-existing renal impairment and in those who receive multiple cycles of bisphosphonate therapy. This recommendation was changed to reflect the new dosing guidelines for patients with pre-existing renal impairment added to the zoledronic acid package insert in January 200512 and the availability of the new bone-modifying agent, denosumab. The zoledronic acid package insert recommends a lower initial zoledronic acid dose (ranging from 3.0 to 3.5 mg) depending on the estimated creatinine clearance. No similar dosing guideline exists for pamidronate. The FDA-approved label for denosumab does not specify a need for dose adjustment for renal safety.13

In addition to the package inserts for denosumab, zoledronic acid, and pamidronate, the evidence reviewed for this recommendation included four RCTs, a safety extension of one of those RCTs, and a retrospective cohort study.

Pamidronate and zoledronic acid should be withheld from patients developing renal deterioration as defined in the package inserts. Once serum creatinine returns to within 10% of baseline, therapy can be resumed. The FDA label states that zoledronic acid therapy should be reinitiated at the same dose as that before treatment interruption. Ibandronate may have a different renal safety profile than pamidronate and zoledronic acid; however, no definitive conclusions about their comparative safety can be reached. Data on the long-term renal safety of bone-modifying agents are limited.

The Update Committee agrees with the FDA package insert directions for use of denosumab, pamidronate, and zoledronic acid, including the monitoring of laboratory parameters, dose, and infusion times. The Update Committee encourages health care providers to be active in reporting postmarketing safety concerns and to review the FDA labeling and Web sites for updates.

Follow-up from the zoledronic acid versus pamidronate studies have not changed the 2003 guideline’s conclusion that the safety of the two agents seems to be similar with respect to nonrenal adverse events. Ibandronate may have a slightly higher risk of GI adverse effects than zoledronic acid or placebo and higher arthralgia than placebo. Denosumab had a lower rate of arthralgia, asthenia, and acute-phase reactions than zoledronic acid and a higher rate of hypocalcemia. Patients
### Table 1. Summary of 2011 Recommendations

<table>
<thead>
<tr>
<th>Recommendation Category</th>
<th>2003 Recommendations</th>
<th>2011 Recommendations</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 1:</strong></td>
<td>For breast cancer patients who have evidence of bone destruction on plain radiographs, IV pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended. Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction, but normal plain radiographs, is considered reasonable by Panel consensus based on the findings in women with lytic or mixed lytic/blastic changes on plain radiographs. There is insufficient evidence relating to efficacy to support one bisphosphonate over the other. For each of the guidelines, clinical judgment should also take into consideration the patient’s general performance status and overall prognosis.</td>
<td>For patients with breast cancer who have evidence of bone metastases, denosumab 120 mg subcutaneously every 4 weeks, IV pamidronate 90 mg delivered over no less than 2 hours, or zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks is recommended. Starting bone-modifying agents in women with an abnormal bone scan and an abnormal CT or MRI showing bone destruction, but normal plain radiographs, is considered reasonable by Panel consensus based on the findings in women with lytic or mixed lytic/blastic changes on plain radiographs. Starting bone-modifying agents in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, CT scans, or MRI is not recommended. This clinical situation has been inadequately studied using IV bisphosphonates or other IV bone-modifying agents and should be the focus of new clinical trials.</td>
<td>Addition of new bone-modifying agent. Term changed from bisphosphonates to bone-modifying agents.</td>
</tr>
<tr>
<td><strong>Recommendation 2:</strong></td>
<td>Starting bisphosphonates in women without evidence of bone metastases even in the presence of other extraskeletal metastases is not recommended. This clinical situation has not been studied using IV bisphosphonates and should be the focus of new clinical trials. Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, CT scans, or MRI is not recommended.</td>
<td>Starting bone-modifying agents in women without evidence of bone metastases even in the presence of other extraoskeletal metastases is not recommended. This clinical situation has been inadequately studied using IV bisphosphonates or other IV bone-modifying agents and should be the focus of new clinical trials.</td>
<td>(Unchanged in substance from 2003)</td>
</tr>
<tr>
<td><strong>Recommendation 3A:</strong></td>
<td>In patients with pre-existing renal disease and a serum creatinine &lt; 3.0 mg/dL (265 μmol/L), no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Use of these bisphosphonates among patients with worse function has been minimally assessed. Infusion times &lt; 2 hours with pamidronate or &lt; 15 minutes with zoledronic acid should be avoided.</td>
<td>In patients with a calculated serum creatinine clearance &gt; 60 mL/min, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid administration is required. Use of bone-modifying agents among patients with reduced renal function has been incompletely assessed. The packet insert of zoledronic acid provides guidance for dosing when baseline serum creatinine clearance is ≥ 30 and &lt; 60 mL/min.</td>
<td>Addition regarding denosumab. A change in serum creatinine clearance threshold. Last sentence of 2003 recommendation taken out.</td>
</tr>
<tr>
<td><strong>Recommendation 3B:</strong></td>
<td>In contrast to multiple myeloma patients, there currently are no data to support routine assessments for albuminuria in patients with breast cancer.</td>
<td>ONJ is an uncommon but potentially serious condition associated with the use of bone-modifying agents. The Update Committee concurs with the revised FDA label for zoledronic acid and pamidronate and the FDA label for denosumab and recommends that all patients with cancer receive a dental examination and necessary preventive dentistry prior to initiating therapy with inhibitors of osteoclast function unless there are mitigating factors that preclude the dental assessment. These recommendations should be observed whenever possible. While receiving inhibitors of osteoclast function, patients should maintain optimal oral hygiene and, if possible, avoid invasive dental procedures that involve manipulation of the jaw bone or periosteum. Although most cases of ONJ have occurred in patients treated with IV bisphosphonates and bone-modifying agents who underwent an invasive dental procedure, cases have occurred spontaneously and have been reported in patients treated with other bone-modifying agents, including oral bisphosphonates and direct osteoclast inhibitors.</td>
<td>New recommendation</td>
</tr>
</tbody>
</table>

*ONJ is an uncommon but potentially serious condition associated with the use of bone-modifying agents. The Update Committee concurs with the revised FDA label for zoledronic acid and pamidronate and the FDA label for denosumab and recommends that all patients with cancer receive a dental examination and necessary preventive dentistry prior to initiating therapy with inhibitors of osteoclast function unless there are mitigating factors that preclude the dental assessment. These recommendations should be observed whenever possible. While receiving inhibitors of osteoclast function, patients should maintain optimal oral hygiene and, if possible, avoid invasive dental procedures that involve manipulation of the jaw bone or periosteum. Although most cases of ONJ have occurred in patients treated with IV bisphosphonates and bone-modifying agents who underwent an invasive dental procedure, cases have occurred spontaneously and have been reported in patients treated with other bone-modifying agents, including oral bisphosphonates and direct osteoclast inhibitors.*
with a creatinine clearance of less than 30 mL/min or receiving dialysis are at a greater risk of severe hypocalcemia than patients with normal renal function.

**Clinical Question 3B**

What are the ONJ safety concerns of bone-modifying agent therapy?

**Literature update and discussion.** This recommendation is new to the guideline. ONJ is defined as an area of exposed bone in the maxillofacial or mandibular region that does not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate administered orally or IV and had not had radiation therapy to the craniofacial region. The exposed bone is necrotic. Risk factors for ONJ include both bisphosphonate type and duration of exposure, with the risk of ONJ increasing with the higher potency drugs (zoledronic acid) and a longer duration of therapy. The risk for ONJ occurs with denosumab, pamidronate, and zoledronic acid, whether administered alone or in sequence with other bone-modifying agents. The true incidence, prevalence, and etiology of ONJ remain unknown and are the subjects of ongoing investigations.

Although direct evidence of the best way to minimize the risk of ONJ during bone-modifying agent treatment is lacking, the guideline recommends care in line with the FDA-approved labeling. The FDA-approved labeling of denosumab, pamidronate, and zoledronic acid advises that patients should maintain good oral hygiene, have preventive dental examinations before initiating therapy, and avoid invasive dental procedures whenever possible, 12-14. Good oral hygiene includes brushing and flossing after meals and use of a fluoride mouth rinse.

The Update Committee, by consensus, suggests that in the setting of invasive dental procedures, it is advisable, whenever possible to delay the starting of therapy with bone-modifying agents until the initial bone healing process of the tooth socket bone has taken place. If an invasive manipulation of the bone underlying the teeth is clinically indicated before starting bone-modifying agent therapy, the Update Committee consensus opinion is that initiation of bone-modifying agent therapy should be ideally delayed for 14 to 21 days to allow for wound healing, if the clinical situation permits.

There were no RCT data to provide support for this recommendation. The evidence cited for this recommendation includes two cohort studies, one case-control study, one chart review, two single-institution experiences, product labels, and position papers, taskforce reports, and reviews and/or position papers from other specialty medical or dental societies. Please refer to the full guideline update for a more extensive discussion of ONJ.
Clinical Question 4

What is the optimal duration of bone-modifying agent therapy for patients with metastatic breast cancer?

Literature update and discussion. This recommendation remains unchanged from 2003. There were no new published prospective clinical trials comparing different durations of bone-modifying agent therapy. In clinical trials, durations of therapy ranged from 12 weeks in an early-phase trial of denosumab to 96 weeks for the bisphosphonates and up to 34 months in the phase III trial of denosumab. These studies do not provide data on the impact of either continuing or stopping bone-modifying agent therapy after a defined time course, the rate of change in SREs in study groups, or the impact of limited versus sustained versus pulsed use of bisphosphonate therapy.

Clinical Question 5

What are the best intervals between dosing?

Literature update and discussion. This recommendation remains unchanged from 2003. There was no new evidence to support a change because most trials have continued using intervals of every 3 to 4 weeks.

Concerns exist regarding the dosing interval and duration of therapy. There are limited data on the local (bone surface) bisphosphonate drug concentrations and retention times. These factors are determined by the cellular status of individual bone surfaces, which is affected by the rate of bone turnover, which is influenced by prior bisphosphonate therapy and the cancer itself.

Because of lack of new evidence, the expert consensus of the Update Committee was to continue to support the 2003 recommendation. The Update Committee recognizes that clinical judgment may dictate modifications to dose schedules for a variety of patient-specific indications.

Clinical Question 6

What is the role of bone-modifying agents in control of pain secondary to bone metastases?

Literature update and discussion. This recommendation remains unchanged from 2003. Bone-modifying agents are an adjunctive therapy for pain control. Pain or the manifestation of an SRE is not necessary for the initiation of a bone-modifying agent in a patient with bone metastases from breast cancer. Zoledronic acid, pamidronate, and IV and oral ibandronate have all been shown to reduce pain scores (primarily based on the Brief Pain Inventory) and analgesic use in patients in three RCTs, two cohort studies, and five analyses of data from RCTs reviewed for this guideline update.

Clinical Question 7

What is the role of biochemical markers of bone turnover to guide initiation of therapy in patients without a prior skeletal event, predict treatment response, guide adjustments to bone-modifying agent therapy, or independently predict future fractures?

Literature update and discussion. This recommendation remains unchanged. Patients with metastatic bone disease and elevated mark-
that explicitly compare different intervals between treatment with bone-modifying agents to learn the effects on relevant clinical outcomes such as SREs, time to SRE, pain, or adverse events evaluated in this guideline.

Trials specific to whether patients with stage IV breast cancer and no bone metastases would benefit from initiating bone-modifying agents are needed. Stratification and analysis by such factors as sex, estrogen receptor/progesterone receptor status, human epidermal growth factor receptor 2 status, ethnic and racial status, and whether a given participant has bone-predominant disease versus visceral-dominant disease could help identify whether any of these factors are relevant in selecting the use of bone-modifying agents. In addition, more research is needed on denosumab and other new bone-modifying agents, the role of biomarkers in treatment selection and monitoring, the role of calcium and vitamin D supplementation, comparative effectiveness research, and how and when bone-modifying agents should be integrated with other therapies.

In addition, although progress has been made in the years since the identification of ONJ to characterize and define the toxicity, much research remains to be performed to better determine and ameliorate risk factors and to offer effective treatment for ONJ associated with bone-modifying agent therapy for breast cancer. Several ongoing and planned studies are gathering data on incidence, risk factors, and treatment of ONJ.

The Update Committee stresses the importance of communicating risks and benefits of and the rationale expected for using bone-modifying agents, including clarifying potential outcomes. The Update Committee also suggests that clinicians give patients opportunities to share their expectations of treatment. In addition, awareness of disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to those in vulnerable populations. Further discussion of patient-clinician communication and health disparities is available in the full guideline.

**PATIENT-CLINICIAN COMMUNICATION AND HEALTH DISPARITIES**

The Update Committee acknowledges the importance of communicating risks and benefits of and the rationale expected for using bone-modifying agents, including clarifying potential outcomes. The Update Committee also suggests that clinicians give patients opportunities to share their expectations of treatment. In addition, awareness of disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to those in vulnerable populations. Further discussion of patient-clinician communication and health disparities is available in the full guideline.

**REFERENCES**


CORRECTIONS

Author Corrections


In Table 1, in the visceral involvement row, the number of patients in the fulvestrant 500 mg treatment group was given as 239 (66%), whereas it should have been 205 (57%). Also, the number of patients in the fulvestrant 250 mg treatment group was given as 232 (62%), whereas it should have been 198 (53%).

In Figure 3, the results depicted for no visceral involvement showed an HR of 0.74 (95% CI, 0.56 to 0.98), whereas it should have been an HR of 0.72 (95% CI, 0.57 to 0.92). Also, the results depicted for visceral involvement represent an HR of 0.82 (95% CI, 0.67 to 1.00), whereas it should have been an HR of 0.86 (95% CI, 0.70 to 1.06).

In the Results section, under Efficacy, an HR of 0.78 (95% CI, 0.67 to 0.92; \(P = .003\)) was given for the PFS analysis in the first sentence of the second paragraph, whereas it should have been an HR of 0.79 (95% CI, 0.68 to 0.93; \(P = .004\)), as follows: “The PFS analysis adjusted by predefined covariates resulted in an HR of 0.79 (95% CI, 0.68 to 0.93; \(P = .004\)).”

In the Discussion section, \(P = .801\) was given for the global interaction test in the second sentence of the fourth paragraph, whereas it should have been \(P = .796\), as follows: “The planned subgroup analysis according to six pre-defined covariates suggests that the type of treatment effect seems to be consistent across the investigated subgroups (global interaction test, \(P = .796\); Fig 3).”

The authors believe that these errors do not affect the overall results and conclusions of the study, and apologize to the readers for the mistakes.

DOI: 10.1200/JCO.2011.36.8522


In Table 1, the column heading “GIMEMA/AML 10” should have been labeled “EORTC/GIMEMA.” Also, in the Abbreviations list, EORTC should have been listed as the European Organisation for Research on Treatment of Cancer.

The authors apologize to the readers for the mistake.

DOI: 10.1200/JCO.2011.36.8530


In the Authors’ Disclosure of Potential Conflicts of Interest section, Catherine Van Poznak’s work as a consultant/advisor for Amgen was listed as compensated (C), whereas it should have been listed as uncompensated (U).

The authors apologize to the readers for the mistake.

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Anti-HER2 neoadjuvant and adjuvant therapies in HER2 positive breast cancer

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SUMMARY

Since the introduction of anti-HER2 agents, the prognosis of HER2 positive breast cancer patients significantly improved. In the adjuvant setting, the monoclonal antibody trastuzumab has been evaluated in six randomized trials including more than 10,000 patients. Different modes of administration (concurrent versus sequential), durations (one year, two years or 9 weeks) and different chemotherapy regimens have been evaluated. To date, one year of trastuzumab in combination or after chemotherapy is the standard adjuvant therapy for patients with HER2 overexpressing tumors. Cardiac safety is still a major clinical issue, in particular in the treatment of early breast cancer. Several large randomized trials exploring shorter, and potentially less toxic, regimens are ongoing across several European countries. In the neoadjuvant setting, the addition of trastuzumab to chemotherapy resulted in a significantly higher activity as compared to chemotherapy alone. Unfortunately, primary and secondary resistance to trastuzumab is observed both in early and advanced disease. Several mechanisms are described as possible determinants of trastuzumab failure, and several new antiHER2 strategies are in development. Lapatinib, the HER1–2 TK inhibitor is currently approved in advanced disease after trastuzumab failure. Lapatinib is under evaluation in a large adjuvant trial, and in several neoadjuvant studies. Other molecules such pertuzumab, which binds the HER2 dimerization domain, or the pan-erbB TK inhibitor neratinib are under evaluation in the (neo)-adjuvant setting.

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Introduction

Human epidermal growth factor receptor 2 (HER2) is overexpressed or amplified in 15–20% of breast tumors, and confers a more aggressive clinical behaviour. However, since the introduction of anti-HER2 agents, first of all the monoclonal antibody trastuzumab, the prognosis of this subset of breast cancer significantly improved.1 In HER2 positive metastatic breast cancer, the addition of trastuzumab to chemotherapy resulted in an improved time to progression, overall response, and duration of response and survival.2,3 In this review, available data on adjuvant and neoadjuvant therapy with standard chemotherapy plus anti-HER2 agents will be reviewed, ongoing trials and new therapeutic options will be discussed.

Summary of adjuvant trastuzumab trials

The results of six phase III randomized trials have been published or reported so far, exploring the benefit of adding trastuzumab to adjuvant chemotherapy for early HER2-positive breast cancer patients. Different administrations of trastuzumab in terms of schedule, timing and duration have been tested. The findings of adjuvant trastuzumab trials are summarized in Table 1. In detail, all experimental arms were designed to give one year of trastuzumab adjuvant therapy with the exception of the HERA trial, where a third arm investigates 2 years of adjuvant trastuzumab, and the FinHER study, planned to explore the efficacy of a shorter period of trastuzumab administration (9 weeks) concurrently with chemotherapy. As of June 2010, no data are yet available for the 2-year trastuzumab arm in the HERA trial. Furthermore, the joint analysis of NSABP B-31 and N9831, the FinHER and the BCIRG006 studies were planned to assess the efficacy of trastuzumab failure, and several new antiHER2 strategies are in development. Lapatinib, the HER1–2 TK inhibitor is currently approved in advanced disease after trastuzumab failure. Lapatinib is under evaluation in a large adjuvant trial, and in several neoadjuvant studies. Other molecules such pertuzumab, which binds the HER2 dimerization domain, or the pan-erbB TK inhibitor neratinib are under evaluation in the (neo)-adjuvant setting.

NSABP B-31 and N9831 trials were included in a planned joint analysis approved by the NCI and FDA: data from both control groups were combined and compared to the concurrent arms of the two trials considered together (group 2 and group C, respectively) and referred to as the trastuzumab group. Group B of trial N9831 was excluded because the protocol required trastuzumab to be administered after the completion of chemotherapy. A total of 394 events in 3351 patients was reached for the first interim analysis, where a significant benefit in disease-free survival (DFS) for the trastuzumab group was observed. Moreover, trastuzumab...
Table 1
Adjuvant trastuzumab trials results

<table>
<thead>
<tr>
<th>Study</th>
<th>Median follow-up</th>
<th>Events</th>
<th>DFS: HR (95% CI), p value</th>
<th>Deaths</th>
<th>OS: HR (95% CI), p value</th>
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<tbody>
<tr>
<td>HERA</td>
<td>Observation vs 1 y sequential H</td>
<td>4 y</td>
<td>827</td>
<td>0.76 (0.66–0.87), p &lt; 0.0001</td>
<td>395</td>
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<td>N9831-NSABP B31 5</td>
<td>AC → T vs AC → T+H</td>
<td>2.9 y</td>
<td>619</td>
<td>0.48 (0.41–0.57), p &lt; 0.00001</td>
<td>258</td>
</tr>
<tr>
<td>N9831 13</td>
<td>AC → T vs AC → T → H</td>
<td>5.5 y</td>
<td>386</td>
<td>0.67 (0.55–0.82), p = 0.0005</td>
<td>220</td>
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<td>BCIRG 006 6</td>
<td>AC → D vs AC → D+H</td>
<td>5.4 y</td>
<td>442</td>
<td>0.64 (0.53–0.78), p &lt; 0.001</td>
<td>235</td>
</tr>
<tr>
<td>PACS-04 12</td>
<td>FEC/D vs FEC/D+H → T</td>
<td>3.9 y</td>
<td>129</td>
<td>0.86 (0.61–1.22), p = 0.41</td>
<td>40</td>
</tr>
<tr>
<td>FinHER 8</td>
<td>D → FEC vs D+H → FEC</td>
<td>5.2 y</td>
<td>18*</td>
<td>0.32 (0.12–0.89), p = 0.029</td>
<td>14</td>
</tr>
</tbody>
</table>

*boundary for significance preset at 0.001; † distant recurrences; ‡ distant disease-free survival.

DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; HERA, Herceptin Adjuvant Trial; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; BCIRG, Breast Cancer International Research Group; PACS, Programme d’Actions Concertées Sein; FinHER, Finnish Herceptin; H, trastuzumab; AC, doxorubicin plus cyclophosphamide; T, paclitaxel; D, docetaxel; Ca, carboplatin; FEC, 5-fluorouracil plus epirubicin plus cyclophosphamide; ED, epirubicin plus docetaxel; NR, not reported; y, years.

therapy was associated with a 33% reduction in the risk of death (P = 0.015). After the release of these findings, crossover from control group to trastuzumab therapy was allowed. At the second interim analysis (3968 patients, median follow up of 2.9 years), the concurrent administration of chemotherapy and trastuzumab versus chemotherapy alone resulted in a 52% reduction in the risk of relapse (P < 0.00001), and in a 35% reduction in the risk of death (P = 0.0007), despite 21% of the patients in the control arm crossed to trastuzumab.5

The BCIRG 006 trial was designed to assess the benefit of adding trastuzumab concurrently to an anthracycline-containing regimen or a non-anthracycline-containing regimen in patients with HER2 positive breast cancer, with the secondary aim to investigate whether the association of trastuzumab, carboplatin and docetaxel could be better tolerated without any loss in terms of efficacy versus the anthracycline-based schedule. Data are available for the last update at a median follow up of 65 months. Both trastuzumab arms demonstrated statistically significant advantages in either DFS or OS versus the control group; no significant difference between the two trastuzumab arms was observed but there was a trend in an event numerical advantage for the anthracycline-based group occurring at the cost of more cardiac events. Among the four major trials, BCIRG 006 registered the lowest rate of cross over (2.1%).9

The third study planned to explore the activity of concurrent trastuzumab and chemotherapy is the FinHER study, where 1010 patients were randomized to receive adjuvant docetaxel or vinorelbine followed by FEC. Patients who had an amplified HER2/neu gene (n = 232) were further randomized to receive trastuzumab concurrently to docetaxel/vinorelbine or not. At a median follow up of 36 months, the inclusion of trastuzumab in the adjuvant chemotherapeutic regimen resulted in a significantly better DFS (HR 0.42 95% CI, 0.21–0.83; p = 0.01); also OS tended to be better, although not significant (p = 0.07).7 The last update of the study, at a median follow up of 5 years, confirmed the benefits of adding a short course of concurrent trastuzumab to docetaxel followed by FEC versus chemotherapy alone (HR for distant disease recurrence 0.32, p = 0.029).8 However, due to the limited sample size, these results need to be confirmed in larger series.

The HERA trial randomized 5102 patients who completed at least 4 courses of adjuvant chemotherapy (anthracycline-taxane combination in 26% of cases only) with or without radiotherapy to receive three-weekly trastuzumab for 1 year or 2 years or to observation. After a median follow up of 12 months, the first interim analysis showed a significantly better DFS for 1 year trastuzumab compared to observation (HR 0.54; 95% CI, 0.43–0.67).9 At this time, patients in the observation group were allowed to cross over to trastuzumab treatment and to choose between 1 or 2 years of treatment. At a median follow up of 23.5 months, with a median time from crossover of 2.8 months, a significant benefit in OS for the trastuzumab arm was observed (HR 0.66; 95% CI, 0.47–0.91; p = 0.115; similar results from intention to treat population and censored analysis).10 The last analysis, after a median follow up of 48 months, demonstrated a persistent significant benefit in DFS for 1 year of trastuzumab versus observation but the difference in OS was not confirmed. To investigate the potential confounding role of crossover at a longer follow up, a further analysis has been conducted among patients in the observation arm that were alive and free of disease in May 2005 (1354), comparing the outcome of patients who crossed over to trastuzumab (65%) to those who did not. Median time to crossover from randomization was 22.8 months. Patients who crossed over to trastuzumab arms seem to have a better DFS and OS, suggesting a potential benefit deriving from later introduction of trastuzumab, but this is an exploratory analysis which may be confounded by patient selection.11

In the PACS-04 study, after a first randomization between epirubicin-docetaxel or FEC, HER2 positive patients (n = 528) were randomly assigned to receive sequential trastuzumab or to observation. At a median follow up of 4 years, the addition of sequential trastuzumab failed to detect a significant reduction in the risk of recurrence or death.12

The only source for a direct comparison between the concurrent and the sequential strategy is the N9831 trial. The sequential administration of trastuzumab and chemotherapy versus chemotherapy alone resulted in a 33% reduction in the risk of recurrence (p = 0.0005), and in a 14% reduction in the risk of death (p = 0.281). A 25% improvement in HR for DFS (p = 0.019) and a 21% reduction in the risk of death (p = 0.135) have been obtained by using trastuzumab concurrently to chemotherapy versus the sequential arm. Therefore the authors recommend the incorporation of trastuzumab in a concurrent fashion.13

In conclusion, sequential adjuvant trastuzumab treatment resulted to be effective in terms of DFS in two of three trials, but no improvement in OS was seen neither in the comparison of control versus sequential arm of the N9831 trial although it was censored for patients who crossed over, nor in the last update of HERA trial; however, the cross over and the fact that most of the patients in the control arm who relapsed received trastuzumab for metastatic disease may have biased the results.
In addition, the negative findings from the PACS-04 trial may be due to a lower activity of trastuzumab therapy especially when given sequentially to an optimal adjuvant chemotherapy, taking into account that in the HERA trial only 26% of the population received an anthracycline-taxane combination. In contrast, the concurrent strategy demonstrated to be more strongly related to benefit in OS in the two major trials that addressed this topic with only minimally increased risk of cardiotoxicity. Furthermore, the direct comparison between the sequential and concurrent arm of the N9831 trial suggested lower risk of an event when starting trastuzumab concomitantly to taxanes.

**Summary of neoadjuvant trastuzumab trials**

Preoperative or neoadjuvant chemotherapy is the standard therapy for inflammatory and locally advanced breast cancer, and it is currently increasingly used also in patients with operable disease. In fact, even if this strategy has not yet produced a survival advantage, as compared to standard postoperative therapy, preoperative chemotherapy can allow for breast conservative surgery when upfront mastectomy is recommended, or can offer a better cosmetic result in case of unfavourable breast-to-tumor size ratio. A meta-analysis of trials comparing preoperative chemotherapy to standard postoperative chemotherapy has shown no significant differences in risk of death, disease progression or distant disease-recurrence between these two strategies. Moreover, the neoadjuvant setting permits an in vivo evaluation of treatment efficacy, and allows to identify subgroups of patients with different prognosis: the patients who achieve a pathological complete response (pCR) benefit most from the treatment and have an excellent prognosis while those who received chemotherapy alone: 87% versus 74% for ORR, respectively (p = 0.009); 38% versus 19% for pCR, respectively (p = 0.001).

In the phase III GeparQuattro trial, 1509 patients with operable or locally advanced tumors were randomized to receive neoadjuvant chemotherapy with four cycles of epirubicin/cyclophosphamide followed by four cycles of docetaxel with or without capecitabine. The 445 HER2 positive patients enrolled received also trastuzumab 6 mg/kg (with a loading dose of 8 mg/kg) every 3 weeks during all chemotherapy cycles. The pCR rate in the HER2+ subset was 31.7%, and no relevant early toxicity was observed.

These data indicate that the upfront administration of trastuzumab in combination with chemotherapy can induce a high pCR rate with no relevant toxicities, and should be considered when neoadjuvant treatment is given to patients with HER2-positive breast cancer.

**Unanswered questions from adjuvant trastuzumab trials**

The phase III NOAH trial evaluated the addition of trastuzumab to an anthracyline- and taxane-based chemotherapy for HER2-positive patients with locally advanced (LABC) or inflammatory breast cancer: 334 patients were randomized to receive three cycles of doxorubicin (60 mg/sqm) and paclitaxel (150 mg/sqm) q3w, 4 cycles of paclitaxel (175 mg/sqm q3w) and 3 cycles of CMF (cyclophosphamide 600 mg/sqm, methotrexate 40 mg/sqm, 5-fluorouracil 600 mg/sqm q4w) on days 1 and 8, with or without concomitant trastuzumab (8 mg/kg loading dose then 6 mg/kg q3w for 1 year) before surgery. In parallel, LABC patients screened as HER2-negative received the same chemotherapy regimen. The primary endpoint was event-free survival (EFS), secondary endpoints were pCR, ORR, OS and safety. EFS rate at 3 years was significantly better in the chemotherapy plus trastuzumab arm compared with chemotherapy alone: 71% versus 56% respectively (HR 0.59, p = 0.013); moreover, both ORR and pCR were significantly higher in the chemotherapy plus trastuzumab arm compared with chemotherapy alone: 87% versus 74% for ORR, respectively (p = 0.09); 38% versus 19% for pCR, respectively (p = 0.001).

In this perspective, the cardiac safety issue appears even more important. In fact, in spite of applying careful patient selection in respect of cardiac function and prior cardiac morbidities, both symptomatic and asymptomatic cardiac dysfunctions have been reported in the majority of large trastuzumab adjuvant trials. Symptomatic congestive heart failure (CHF) occurred in 1.5–2.5% of the patients treated with sequential trastuzumab, and in 0.4–3.6% of the patients treated with concomitant chemotherapy and trastuzumab (the lowest observed BCRG 006 arm C, not including antracyclines). The FinHer trial is the only adjuvant trastuzumab trial without episodes of CHF. More recently, some data are emerging supporting the non complete reversibility of trastuzumab related cardiac dysfunction. Taking into account the absence of long term follow up, the clinical impact of asymptomatic LVEF decline on long term cardiac morbidity and mortality is still...
unknown. The optimal trastuzumab duration is still a matter of debate; the choice of 1 year administration in the adjuvant trials has an empirical basis only. The data from the 2-year arm of HERA are still lacking. Exploring potentially less toxic regimens remains a major clinical issue. Several large randomized trials exploring shorter trastuzumab duration are ongoing across several European countries (the Phare trial in France, the Sold trial in Finland and other north European countries, The Persephone trial in UK, and The Short-Her trial in Italy). 30

New combinations in the treatment of HER2 positive early breast cancer

Despite the major advance obtained with the introduction of trastuzumab in clinical daily practice, primary and secondary resistance to trastuzumab is observed both in early and advanced disease. Several mechanisms are described as possible determinants of trastuzumab failure. The expression of a truncated form of HER2, the p95-Her2, which is lacking the extra-membrane domain, is emerging as a marker of trastuzumab primary resistance. Other molecules involved in HER2 dependent signal transduction pathway, such as PTEN, PI3KCA are also involved in resistance to anti-HER2 agents. 31 The dual TK inhibitor of HER1 and HER2 lapatinib is currently approved for the treatment of metastatic breast cancer failing trastuzumab therapy, and several new anti-HER2 agents are in advanced clinical development. Lapatinib, by acting at the intracellular TK domain, seems able to overcome trastuzumab resistance derived from p95 expression. 32

A large phase III randomized adjuvant study, the ALTTO trial, is comparing the activity of lapatinib alone versus trastuzumab alone versus trastuzumab followed by lapatinib versus the combination of lapatinib administered concomitantly with trastuzumab.

Several neoadjuvant studies are ongoing. The phase III NeoALTTO study, which compares neoadjuvant taxane-based chemotherapy plus trastuzumab, lapatinib or both, has completed the accrual. In the HER2 positive cohort of the Geparquinto randomized study, patients are randomly assigned to sequential chemotherapy consisting of epirubicin-cyclophosphamide followed by docetaxel plus either lapatinib or trastuzumab. The phase II randomized CHERLOB study is about to complete the enrolment. In this study, the activity in terms of pCR rate (defined as absence of infiltrating residual disease in breast and axillary nodes) of neoadjuvant lapatinib, trastuzumab or both lapatinib and trastuzumab in combination with an anthracycline-taxane sequential chemotherapy (weekly paclitaxel followed by FEC) is evaluated. Preliminary activity and safety data have been presented: the overall pCR rate is 37.5%; no cardiac safety concern has emerged until now by combining anthracycline with trastuzumab and/or lapatinib. 33

Pertuzumab is a monoclonal antibody directed against the dimerization domain of HER2. This agent has provided interesting activity in metastatic breast cancer: A phase II, four arms randomized trial, the Neosphere trial, is exploring different neoadjuvant combinations including pertuzumab, trastuzumab and docetaxel. The Neosphere study has completed the accrual, and data will be available by the end of 2010. Another interesting molecule is the pan-erbB inhibitor neratinib. This is a small molecule, irreversible TK inhibitor of HER1, 2 and 4. A large randomized, double blind, placebo-controlled adjuvant study is ongoing. In this study, patients who have completed adjuvant trastuzumab no longer than 2 years before and free from recurrence will be randomly assigned to neratinib versus placebo for one year.

Conflict of interests

Valentina Guarneri: speaker for GlaxoSmithKline. Elena Barbieri, Maria Vittoria Dieci, Federico Piacentini: none to declare. PierFranco Conte: research grant from GlaxoSmithKline; consultant and speaker for GlaxoSmithKline and Roche.

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