HER2陽性転移性乳がんにおける重要な進歩（Abstract # S5-5）

CLEOPATRA: 二重HER2遮断は転移性乳がん患者の無増悪生存期間を有意に延長する

CLEOPATRA: Dual HER2 blockade significantly extends progression-free survival in metastatic breast cancer

トラスツズマブとドセタキセルの併用化学療法にpertuzumabを追加することによりHER2陽性転移性乳がん患者の無増悪生存期間中央値が6.1ヵ月延長したとの研究結果が、2011年CTRC-AACRサンアントニオ乳がんシンポジウムで発表されNew England Journal of Medicineに掲載された。研究者らはCLEOPATRA（CLinical Evaluation Of Pertuzumab And TRAstuzumab[Pertuzumabとトラスツズマブの臨床的評価]）として知られる国際phase 3、二重盲検、無作為化トライアルを行った。このトライアルでは808人の患者をトラスツズマブとドセタキセルの併用化学療法にpertuzumabまたはプラセボを追加する群に無作為に割り付けた。無増悪生存期間は、pertuzumab群で18.5ヵ月であったのに対しプラセボ群では12.4ヵ月であった―増悪リスクは38%低下した。客観的奏効率（少なくとも30%の腫瘍縮小）は、併用化学療法にpertuzumabを追加することにより80.2%であったのに対し、併用化学療法単独では69.3%であった。生存期間に関する成績は不完全ではあるが、3剤併用群では402人中69人が死亡し、2剤併用群では406人中96人が死亡した。3剤併用療法の忍容性は高かった。Pertuzumabは"二量体化阻害剤"と呼ばれる新たなクラスの初めての薬剤である。

Full Text

Adding pertuzumab to a combination of trastuzumab and docetaxel chemotherapy extended progression-free survival by a median of 6.1 months in patients with metastatic HER2-positive breast cancer compared with patients who received the combination therapy with placebo according to research presented at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium and published in the New England Journal of Medicine.

Researchers conducted an international phase 3, double-blind, randomized trial, known as CLEOPATRA (CLinical Evaluation Of Pertuzumab And TRAstuzumab), in which they randomly assigned 808 patients to receive trastuzumab and docetaxel chemotherapy with pertuzumab or placebo. Progression-free survival (PFS) was 18.5 months for patients who received pertuzumab compared with 12.4 months for patients who received placebo - a 38 percent reduction in risk for progression.

The findings represent a significant advance in the treatment of this advanced breast cancer, said senior researcher José Baselga, M.D., Ph.D., professor in the department of medicine at Harvard Medical School, associate director of the Massachusetts General Hospital Cancer Center and chief of hematology/oncology at Massachusetts General Hospital.

"This is huge. It is very uncommon to have a clinical trial show this level of improvement in PFS," said Baselga. "Most metastatic patients with HER2-positive breast cancer eventually stop responding to trastuzumab, so the fact that we now have an agent that can be added to current treatment to delay progression is very exciting. With the advent of trastuzumab and now pertuzumab, we have come a very long way in treating a type of breast cancer that once had a very poor prognosis."

Pertuzumab is designed to work in combination with trastuzumab as a dual blockade of the HER2 growth factor, which fuels about one third of all breast tumors. Both drugs are monoclonal antibodies that bind to the HER2 receptor protein in different locations. Pertuzumab's role is to prevent the receptor from linking to HER3 and therefore forming a "dimer" that further signals tumor growth - making pertuzumab the first in a new class of drugs called "dimerization inhibitors," Baselga said. "These two agents offer a dual HER2 blockade, shutting down different mechanisms responsible for HER2 signaling."

Adding pertuzumab to the combination therapy resulted in an objective response rate (tumor shrinkage of at least 30 percent) of 80.2 percent compared with 69.3 percent for the combination therapy alone.

Although survival outcomes are not mature, Baselga reported 69 deaths among the 402 patients treated with the three-drug combination and 96 deaths among the 406 patients who received two drugs.

He added that the three-drug combination is "remarkably safe and well tolerated. Only minimal side effects were seen with the addition of pertuzumab." Some of those effects were grades 1 and 2 diarrhea and neutropenia, but no additional cardiac toxicity was seen, he said.

Enrollment is already underway in a new double-blind, randomized clinical trial, APHINITY, to test the use of pertuzumab as adjuvant treatment for early-stage HER2-positive breast cancer. "It is in that setting that you can really cure patients," Baselga said.

TOPICS

エキセメスタンとエベロリムス併用の有効性が確認された（Abstract # S3-7）

BOLERO-2：エキセメスタンとエベロリムスの併用により転移性乳がん女性の無増悪生存期間が上昇した

BOLERO-2: Exemestane plus everolimus increased progression-free survival for women with metastatic breast cancer

ホルモン受容体（HR）陽性の転移性乳がんを有する閉経後女性に対し、エベロリムスとエキセメスタンの併用は疾患コントロール期間を著明に改善したとの、phase3臨床試験、経口エベロリムス乳がんトライアル（Breast Cancer Trials of Oral Everolimus [BOLERO-2]）の結果が2011年CTRC-AACRサンアントニオ乳がんシンポジウムで発表された。研究者らはHR陽性転移性乳がんを有しアナストロゾールまたはレトロゾール投与中に疾患が進行した閉経後女性724人を組み入れた。患者はエキセメスタンとエベロリムスの併用療法またはエキセメスタンとプラセボを投与する群に無作為に割り付けられた。その結果、エキセメスタンとプラセボを投与された患者239人の無増悪生存期間中央値は3.2ヵ月であった。エキセマスタンとエベロリムスの併用療法を受けた患者485人においては、無増悪生存期間中央値は7.4ヵ月と有意であった。完全寛解、部分寛解、または6ヵ月を超える疾患の安定などの臨床有効率は、エキセメスタンとプラセボを投与した患者の25.5%に認められたのに対し、エキセメスタンとエベロリムスの併用療法群では50.5%であった。BOLERO-2の生存期間に関する解析はまだできていない。しかし、治療の忍容性は良好であり、最も多い副作用は口腔粘膜炎、倦怠感、肺炎および高血糖であった。

Full Text

Everolimus in combination with exemestane has shown promise for the treatment of breast cancer.

"For postmenopausal patients with hormone receptor (HR)-positive metastatic breast cancer, the addition of everolimus to exemestane markedly improves the duration of disease control," said Gabriel N. Hortobagyi, M.D., FACP, professor of medicine, chair of the department of breast medical oncology and director of the Multidisciplinary Breast Cancer Research Program at the University of Texas MD Anderson Cancer Center in Houston.

Hortobagyi presented findings from Breast Cancer Trials of Oral Everolimus (BOLERO-2), a phase 3 clinical trial, at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium, held Dec. 6-10, 2011.

BOLERO-2 researchers enrolled 724 postmenopausal patients with HR-positive metastatic breast cancer and evidence of progressive disease while receiving anastrozole or letrozole. They randomly assigned patients to treatment with exemestane plus everolimus or with exemestane plus placebo.

Results revealed a median progression-free interval of 3.2 months for 239 patients treated with exemestane plus placebo. Among the 485 patients treated with exemestane plus everolimus, researchers found a median progression-free interval of 7.4 months, "a highly significant difference," Hortobagyi said.

Clinical benefit rates, which include complete response, partial response, or stable disease exceeding six months, were 25.5 percent among patients treated with exemestane and placebo and 50.5 percent among those treated with exemestane and everolimus.

"The original hypothesis predicted this increased benefit from the combination, based on compelling preclinical experiments and preliminary results from earlier, smaller clinical trials. These results establish a new standard of care for this group of patients," Hortobagyi said.

He continued, "These results highlight the progress being made in understanding the evolving mechanisms of resistance to standard therapies."

Researchers were not yet able to measure survival analysis in BOLERO-2. However, treatment was well tolerated, with oral mucositis, fatigue, pneumonitis and hyperglycemia being the most common side effects.

TOPICS

BRCA変異と対側乳がんのリスク（Abstract # S4-2）

BRCA変異を有する乳がん既往者において対側の新たな乳がんを発症するリスクが高い

Risk for developing contralateral new cancer increased for survivors with BRCA mutation

BRCA1またはBRCA2遺伝子変異を有する乳がん既往者は対側の乳がん（CBC）を発症するリスクが高く、この群の女性の一部は診断時年齢および最初の腫瘍の状態によってさらにリスクが高いとのデータが2011年CTRC-AACRサンアントニオ乳がんシンポジウムで発表された。研究者らは、オランダの10の病院で片側の浸潤性がんと診断された女性5,061人を調査した。211人（4.2%）がBRCA1またはBRCA2のキャリアであった。フォローアップ期間中央値8.4ヵ月の時点で、全体の8.6%がCBCを発症した。10年間のCBC総発症率はノンキャリアで6.0%であり、一方キャリアのリスクは17.9%であった。最初の乳がんを40歳未満で診断されたキャリアの10年間のCBCリスクは26.0%に跳ね上がった。40～50歳に最初の乳がんを診断されたキャリアのリスクは11.6%であった。さらに、最初の腫瘍がトリプルネガティブであった変異キャリアの10年間累積CBCリスクは18.9%であり、それと比較し最初の腫瘍がトリプルネガティブでなかったキャリアにおいては11.2%であった。

Full Text

Breast cancer survivors who carry the BRCA1 or BRCA2 genetic mutation are at high risk for developing contralateral breast cancer, and certain women within this group of carriers are at an even greater risk based on age at diagnosis and first tumor status, according to data presented at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium.

"Our studies show that certain subgroups of women [with this mutation] who have already had cancers are also at risk for developing a second new cancer in their other breast, much more so than survivors who do not carry the mutation," said Alexandra J. van den Broek, M.Sc., a doctoral candidate at the Netherlands Cancer Institute. "Our study is, as far as we know, the first study showing that within certain carriers of BRCA mutations, subgroups with an increased or decreased risk for contralateral breast cancer (CBC) can be made."

Researchers surveyed 5,061 women diagnosed with unilateral, invasive breast cancer at 10 hospitals in the Netherlands. Two hundred eleven women (4.2 percent) were carriers of the BRCA1 or BRCA2 mutation. Overall, at a median of 8.4 years of follow-up, 8.6 percent of participants developed CBC.

Van den Broek and colleagues found that the overall 10-year risk for developing CBC in noncarriers was 6.0 percent, while risk for carriers was 17.9 percent.

For carriers diagnosed with their first breast cancer when aged younger than 40 years, the 10-year risk for CBC jumped to 26.0 percent. For carriers between the ages of 40 and 50 years at first diagnosis, the risk was 11.6 percent. In addition, mutation carriers with a triple-negative first tumor had a 10-year cumulative CBC risk of 18.9 percent compared with 11.2 percent among carriers with a non-triple-negative first tumor.

Although these numbers can be overwhelming to carriers who have already survived breast cancer, van den Broek said it is crucial to know who is most at risk and by how much.

"Guidelines for prophylactic measures and screening in the follow-up of patients with breast cancer carrying the BRCA1 or BRCA2 mutation are important to provide patients with the best information and counseling," she said. "If these results are confirmed, [it will be] possible to personalize the guidelines for these specific subgroups."

The next step will be to confirm the results in larger studies and to look at other factors that define subgroups of patients with an increased or decreased risk for CBC.

TOPICS

早期のビスフォスフォネート投与は遅延した投与に勝る（Abstract＃S1-3）

ZO-FAST：内分泌療法直後のゾレドロン酸投与により閉経後早期乳がん患者の再発が減少し生存率が上昇した

ZO-FAST: Immediate zoledronic acid use with endocrine therapy reduced recurrence, increased survival in postmenopausal early breast cancer

アジュバント内分泌療法にゾレドロン酸を追加することにより、ホルモン受容体陽性早期乳がんを有する閉経後女性の骨塩密度が上昇し乳がん再発リスクが低下した、と2011年CTRC-AACRサンアントニオ乳がんシンポジウムで発表された。研究者らは、アロマターゼ阻害薬レトロゾール開始直前の患者1,065人を、直後にゾレドロン酸を6ヵ月ごとに投与する群と、患者が骨折や明らかな骨密度低下を認めた場合のみゾレドロン酸を後に開始する群とに無作為に割り付けた。60ヵ月後にトライアルの一次エンドポイント達成に成功した―直後のゾレドロン酸投与により腰椎および骨盤骨密度喪失が有意に減少した。ゾレドロン酸を直後に投与された患者においては再発が34%少なく、二次エンドポイントである無病生存期間もまた改善した。診断時に真に閉経後であった女性においては、直後のゾレドロン酸により乳がん再発リスクが29%低下し、全生存期間が35%改善した。

Full Text

The addition of zoledronic acid to adjuvant endocrine therapy increased bone mineral density and reduced the risk for disease recurrence among postmenopausal women with early hormone receptor-positive breast cancer, according to new data from the ZO-FAST trial.

Richard de Boer, M.D., of the Royal Melbourne Hospital in Victoria, Australia, presented long-term data from the Zometa-Femara Adjuvant Synergy Trial (ZO-FAST) at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium.

De Boer and colleagues explored adding zoledronic acid, an intravenous bisphosphonate, to adjuvant endocrine therapy to reduce bone mineral density loss seen with aromatase inhibitors and to improve survival outcomes.

When he presented initial data from ZO-FAST at the 2010 CTRC-AACR San Antonio Breast Cancer Symposium, de Boer indicated that early zoledronic acid resulted in a significantly improved bone mineral density and an improved disease-free survival. At this year's symposium, he reported long-term data and data on the effect of menopausal status at breast cancer diagnosis on disease-free survival.

Researchers randomly assigned 1,065 patients who were about to commence letrozole, an aromatase inhibitor, to receive immediate zoledronic acid every six months or to a delayed group where zoledronic acid was started at a later time only if the patient experienced a fracture or a documented fall in bone mineral density.

After 60 months of follow-up, "the primary endpoint of the trial was successfully achieved - up-front zoledronic acid significantly decreased bone mineral density loss in both the lumbar spine and the hip," de Boer said. "The secondary endpoint of an improvement in disease-free survival was also met with a 34 percent decrease in disease recurrence in the patients receiving the up-front zoledronic acid."

Researchers conducted an exploratory subgroup analysis based on menopausal status at the time of breast cancer diagnosis. Data indicated that in women who were truly menopausal at diagnosis, immediate treatment with zoledronic acid reduced the risk for disease recurrence by 29 percent and improved overall survival by 35 percent.

"In addition, patients in the delayed group, who did not start with zoledronic acid but who switched to start at a later time, also appeared to benefit from the zoledronic acid with an improvement in disease outcomes compared with those women who never started the bisphosphonate," de Boer said.

Additional studies are needed to fully define the patient populations most likely to benefit from adjuvant zoledronic acid in this setting.

Until then, "patients with hormone receptor-positive breast cancer who are postmenopausal and about to commence letrozole have the option of considering the addition of zoledronic acid - primarily to maintain bone mineral density but also with the aim of reducing the risk for disease recurrence," de Boer said.

TOPICS

ゾレドロン酸の乳がんに対する有効性が確認された(Abstract # S1-2)

ABCSG-12：閉経前ER陽性乳がん女性の生存におけるゾレドロン酸の長期有益性が示された

ABCSG-12: Zoledronic acid shows long-term benefit in survivorship for premenopausal ER-positive breast cancer

エストロゲン受容体陽性の閉経前乳がん患者を、卵巣機能抑制を含むアジュバント内分泌治療に加えアジュバントゾレドロン酸により治療することの持続的な有効性が証明された。オーストラリア乳がん＆大腸がんスタディグループ(Austrian Breast & Colorectal Cancer Study Group[ABCSG-12])のデータが2011年CTRC-AACRサンアントニオ乳がんシンポジウムで報告され、過去に報告されたデータが確認および追加された。現在フォローアップ84ヵ月の時点で、毒性副作用はなく患者らの乳がん再発は劇的に減少し生存率は改善した。研究者らはこの4群トライアルにおいて、早期のエストロゲン受容体(ER)陽性乳がんの閉経後女性1,803人を、タモキシフェンまたはアナストロゾールまたは各々とゾレドロン酸を3年間投与される群に無作為に割り付けた。治療の84ヵ月後に、ゾレドロン酸投与群において再発率は28%低下し死亡リスクは36%低下した。また、想定完全卵巣遮断療法を受けた40歳以上の患者では再発リスクが34%低下し死亡リスクは44%低下した。40歳未満の女性においては生存に関する有意な利益は認められなかった。下顎骨壊死や腎不全の発現はみられなかった。

Full Text

Researchers have proven the continuing effectiveness of treating patients with estrogen receptor-positive premenopausal breast cancer with adjuvant zoledronic acid in addition to adjuvant endocrine treatment including ovarian function suppression.

Data from the Austrian Breast & Colorectal Cancer Study Group (ABCSG-12), reported at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium, held Dec. 6-10, 2011, confirmed and extended data reported at 48 months and 62 months of follow-up. Now at 84 months of follow-up, patients are experiencing drastically fewer recurrences of breast cancer and improved rates of survivorship without toxic side effects.

"We have confirmed what this trial showed initially, which was both exciting and surprising," said Michael Gnant, M.D., professor of surgery and president of the ABCSG at the Medical University of Vienna. "The continued success of this treatment means we can intervene early and still observe persistence of the benefit of treatment."

In the four-arm trial, researchers randomly assigned 1,803 premenopausal patients with early-stage, estrogen receptor (ER)-positive breast cancer to receive tamoxifen or anastrazole or each of these two treatments with zoledronic acid for three years. In the initial report, presented in 2008, Gnant and his colleagues reported significantly improved disease-free survival.

The most recent long-term data, at 84 months after treatment, revealed a 28 percent reduced risk for recurrence and a 36 percent reduction in risk for death among patients treated with zoledronic acid. Also, no patients experienced osteonecrosis of the jaw or renal failure - thus, Gnant said, proving the safety of the treatment seven years later.

Researchers also found that patients aged older than 40 years with presumed complete ovarian blockade had a 34 percent reduced risk for recurrence and a 44 percent reduced risk for death. They found no significant survival benefits among patients aged younger than 40 years.

Gnant and his team said these data, considered with previously demonstrated bone-protective effects of zoledronic acid, suggest that adding zoledronic acid to adjuvant endocrine therapy including ovarian function suppression should be considered for premenopausal women with ER-positive early breast cancer.

TOPICS

DCIS患者の再発リスクを予測する新たな検査（Abstract # S4-6）

複数遺伝子アッセイは非浸潤性乳管がん局所再発リスクを予測する

Multigene assay predicts risk for local recurrence for patients with ductal carcinoma in situ

非浸潤性乳管がん（DCIS）患者治療の有意な進歩として、乳がん再発リスクを発見する複数遺伝子検査が開発され前向きに検証された、と2011年CTRC-AACRサンアントニオ乳がんシンポジウムで報告された。この方法は、腫瘍の遺伝子発現計測と遺伝子発現アルゴリズムを組み合わせて、患者のがんの遺伝子基盤を解読し、個々の患者が手術（通常乳腺腫瘍摘出術）で治療されるべきか手術と放射線治療とで治療されるべきかを決定する。研究者らは、オンコジーンDX乳がんアッセイとDCISスコアアルゴリズムを用いて327人の患者の腫瘍を検査およびスコア化し、再発リスクを決定する研究を行った。分子基盤のアッセイを用いた結果、研究者らは再発リスクの高い患者およびリスクの低い患者の同定に成功した。彼らはまたE5194試験の10年間の結果を報告した。この試験において46人が同側乳房イベント（IBE、フォローアップ期間中央値8.8年）を発現した。タモキシフェン使用で補正すると、持続的DCISスコアとIBEには有意な相関が認められ、腫瘍サイズ、腫瘍グレードおよびマージンの状態などの従来の計測値を超える価値を有していた。多くのスタディの結果、ルーチンの顕微鏡的病理学的グレーディングは信頼できる再発リスクのインディケーターではないことが示されている。

Full Text

In a significant advance for patients with ductal carcinoma in situ, researchers have developed and prospectively validated a multigene test to identify the risk for recurrence of breast cancer.

The method combines measuring tumor gene expression with a gene expression algorithm to decipher the genetic underpinnings of a patient's cancer and determine whether the individual patient should be treated with surgery (usually lumpectomy) or a combination of surgery and radiation.

This is the first time a multigene test has been used to differentiate lower-risk and more aggressive forms of ductal carcinoma in situ (DCIS) and will allow physicians to spare many patients the need to undergo radiation, according to researchers.

Lawrence J. Solin, M.D., FACR, FASTRO, chair of the department of radiation oncology at Einstein Medical Center in Philadelphia, presented the results at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium (SABCS).

"Using a molecular-based assay, we have successfully identified patients at higher risk for recurrence and patients at lower risk," said Solin. "This is an important advance for women with newly diagnosed DCIS. By predicting individual risk, physicians can provide a more tailored treatment program for each patient."

The validation study of the DCIS Score was a collaboration among the Eastern Cooperative Oncology Group (ECOG), North Central Cancer Treatment Group and Genomic Health. The validation utilized patient tumor samples from E5194, an ECOG-led, multi-institutional study of patients with low-, intermediate- or high-grade DCIS who had been treated surgically but had not received radiation. E5194 was the first prospective study of local excision alone for DCIS, and its five-year results were reported at SABCS in 2006 (L. Hughes).

Researchers tested and scored tumors from 327 patients to determine their risk for recurrence. The DCIS validation study team used the Oncotype DX breast cancer assay, which has been available for invasive breast cancer since 2004, and a DCIS Score algorithm to study these tumor samples.

The test uses reverse transcriptase-polymerase chain reaction technology, which quantitates the level of RNA in the individual tumor sample to reveal its underlying biology. The level of RNA is then used by a prespecified algorithm to calculate a DCIS Score, which predicts the likelihood of local recurrence, defined as either the development of a new invasive breast cancer or the recurrence of DCIS.

Solin also reported 10-year results of E5194, in which 46 patients had an ipsilateral breast event (IBE; defined as ipsilateral local recurrence of DCIS or invasive cancer) at a median follow-up of 8.8 years. Continuous DCIS Score was significantly associated with IBE when adjusted for tamoxifen use and provided value beyond the traditional measures of tumor size, tumor grade and margin status.

Numerous studies, including the current study, have shown that routine, microscopic pathology grading is not a reliable indicator of the risk for recurrence.

"The DCIS Score will help physicians understand the underlying biology of DCIS for an individual patient and accurately gauge the risk for that person," said Solin. "As a result, the patient and physician can decide on the appropriate course of treatment based on a more complete understanding of the risk involved."

TOPICS