タモキシフェン術後補助療法は5年間より10年間の方が優れている（Abstract # S1-2）

ATLAS：タモキシフェン術後療法を10年間に延長することにより乳がんの遅発性再発リスクが軽減し生存期間が改善した

ATLAS: Extending duration of adjuvant tamoxifen treatment to 10 years reduced risk for late breast cancer recurrence and improved survival

10年間のタモキシフェン術後補助療法は現在の標準的な5年間のタモキシフェン投与と比べ、エストロゲン受容体（ER）陽性乳がん女性に対する遅発性再発および乳がん死からの保護効果が高いとの国際的な研究—Adjuvant Tamoxifen — Longer Against Shorter（ATLAS）の結果が示された。この結果は2012 CTRC-AACRサンアントニオ乳がんシンポジウムで発表され同時に*Lancet*に掲載された。研究者らはER陽性乳がん女性6,846人を組み入れた。半数はリンパ節転移陽性でありタモキシフェンを5年間投与されていた。患者はさらに、5年間治療を継続する群またはそこで治療を中止する群に無作為に割り付けられた。診断後5～9年間の再発率や死亡率に対して治療群による違いは少なかった。しかし、診断後10年目以降20年目まででは、タモキシフェンを継続した女性は5年後に中止した女性よりも再発率が25%低く、乳がん死亡率が29%低かった。診断後5～14年の乳がん死リスクは、治療を継続した者で12.2%であったのに対し、中止した者では15%であった—absolute gainは2.8%であった。最も有益性が高いのは診断後10～14年であった。

Full Text

Ten years of adjuvant treatment with tamoxifen provided women with estrogen receptor-positive breast cancer greater protection against late recurrence and death from breast cancer compared with the current standard of five years of tamoxifen, according to the international ATLAS (Adjuvant Tamoxifen — Longer Against Shorter) study.

"Five years of adjuvant tamoxifen is already an excellent treatment that substantially reduces the 15-year risk for recurrence and death from estrogen receptor (ER)-positive breast cancer, but ATLAS now shows that 10 years of tamoxifen is even more effective," said Christina Davies, M.D., a coordinator in the Clinical Trial Service Unit at the University of Oxford in the United Kingdom.

She presented the results at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium. The results were simultaneously published in the *Lancet*.

"The main additional benefit from continuing tamoxifen treatment is to reduce breast cancer mortality during the second decade after diagnosis," Davies said. "We already knew that five years of tamoxifen reduces breast cancer mortality in this late period by almost a third in comparison with no tamoxifen. We now know that 10 years of tamoxifen is even better, approximately halving breast cancer mortality during the second decade after diagnosis."

Researchers enrolled 6,846 women with ER-positive breast cancer between 1996 and 2005. Half had node-positive disease. All the women had been using tamoxifen for five years, and the researchers randomly assigned them to continue treatment for another five years or to stop immediately.

After about eight years of follow-up, the researchers observed 1,328 breast cancer recurrences and 728 deaths after recurrence. The treatment allocation had little effect on either recurrence rates or death rates during the period five to nine years after diagnosis. However, during the second decade following diagnosis, the women who continued tamoxifen treatment had a 25 percent lower recurrence rate and a 29 percent lower breast cancer mortality rate compared with women who stopped after five years.

Risk for death from breast cancer five to 14 years after diagnosis was 12.2 percent among those who continued use versus 15 percent among those who stopped — an absolute gain of 2.8 percent. The researchers observed the greatest benefit during 10 to 14 years after diagnosis.

Davies noted that continuing tamoxifen use can increase side effects, with endometrial cancer being the most life threatening. Because endometrial cancer is generally curable, the cumulative risk for death between five and 14 years after diagnosis was 0.4 percent versus 0.2 percent. Because this risk is heavily outweighed by the reduction in breast cancer deaths, overall mortality was significantly reduced by longer treatment. In premenopausal women, for whom tamoxifen is often the endocrine treatment of choice, there was no apparent excess of endometrial cancer.

"Many women with ER-positive breast cancer take tamoxifen, or some other adjuvant endocrine treatment, but the current recommendation is to stop after five years," said Davies. "ATLAS showed that protection against breast cancer recurrence and death is greater with 10 years than with five years of tamoxifen use. Women and their doctors should be aware of this evidence when deciding how long to continue tamoxifen, or any other endocrine treatment."

The study was funded by Cancer Research U.K., the U.K. Medical Research Council, AstraZeneca, the United States Army and the European Union.

TOPICS

局所再発後の化学療法は生存期間を延長する（Abstract # S3-2）

乳がんの局所または領域再発部位の外科的完全切除後の化学療法は生存率を上昇させた

Chemotherapy after complete surgical removal of local or regional breast cancer recurrence increased survival rates

術後補助化学療法は孤発性の局所または領域再発乳がん女性の無病生存率および全生存率を上昇させたとのデータが2012 CTRC-AACRサンアントニオ乳がんシンポジウムで発表された。研究者らは孤発性の局所または領域再発を有する患者162人を評価した；85人は術後補助化学療法を施行され、77人は施行されなかった。5年無病生存率は術後補助化学療法を施行された女性で69%であり、施行されなかった女性では57%であった。全生存率は化学療法を施行された患者で88%であり、施行されなかった患者では76%であった。エストロゲン受容体（ER）陰性乳がん女性において有益性が最も高く、5年無病生存率は化学療法を施行された群で67%であり、施行されなかった群では35%であった。さらに、これらの患者群においては、化学療法を施行された群の全生存率は79%であり、施行されなかった群では69%であった。ER陽性患者においては、5年無病生存率は化学療法を施行された群で70%であり施行されなかった群では69%であった。ER陽性患者全生存率は化学療法を施行された群で94%であり施行されなかった群では80%であった。

Full Text

Adjuvant chemotherapy led to higher rates of disease-free and overall survival for women with isolated local or regional recurrence of breast cancer, according to data presented at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium.

Patients with isolated local and/or regional recurrence of their breast cancers are at high risk for developing metastases in other areas of the body. Some physicians administer chemotherapy to these patients after their recurrent tumors have been completely removed by surgery, but the efficacy of this treatment had not been studied until now.

"This is the first randomized controlled study that shows that adjuvant chemotherapy works in these patients," said Stefan Aebi, M.D., head of the division of medical oncology at Luzerner Kantonsspital in Luzern, Switzerland.

He and his colleagues from the Breast International Group, the National Surgical Adjuvant Breast and Bowel Project and the International Breast Cancer Study Group evaluated 162 patients with isolated local and regional recurrence; 85 received adjuvant chemotherapy and 77 did not.

Five-year disease-free survival rates were 69 percent for women who received adjuvant chemotherapy and 57 percent for those who did not. The overall survival rate was 88 percent for women who received chemotherapy compared with 76 percent for those who did not.

Women with estrogen receptor (ER)-negative breast cancer demonstrated the greatest benefit, with a five-year disease-free survival rate of 67 percent among those who received chemotherapy versus 35 percent among those who did not. In addition, within this group, overall survival rates were 79 percent among those who received chemotherapy and 69 percent among those who did not.

For patients with ER-positive disease, five-year disease-free survival was 70 percent for those who received chemotherapy versus 69 percent for those who did not. Overall survival was 94 percent for those patients with ER-positive disease who received chemotherapy versus 80 percent among those who did not.

Aebi recommended that physicians prescribe adjuvant chemotherapy for patients with isolated local and regional recurrence of breast cancer, especially if the recurrence is ER-negative and therefore not sensitive to endocrine therapy.

This research was funded by the National Cancer Institute, the Swiss Cancer League and other national cancer research agencies.

TOPICS

乳がん放射線治療後の局所再発率低下が認められた（Abstract # S4-1）

UK START：10年のフォローアップの結果、早期乳がん治療のための小分割放射線療法は安全で有効であった

UK START: Hypofractionated radiotherapy was safe and effective for early breast cancer treatment at 10-year follow-up

適正線量の小分割放射線療法は健康組織への負担が軽く局所ー領域早期乳がんコントロールに有効であるとのU.K. Standardization of Breast Radiotherapy Trials（START）の結果が、2012 CTRC-AACRサンアントニオ乳がんシンポジウムで発表された。1999～2002年の間に浸潤性乳がんを完全切除された女性4,451人がSTART AまたはSTART Bいずれかの無作為化コントロールトライアルに組み入れられた。START Aでは術後放射線療法を50Gy（25 fraction）で5週間にわたり施行される群と、41.6Gy（13 fraction）または39Gy（13 fraction）を5週間にわたり施行される群とを比較した。START Bでは50Gy（25 fraction）で5週間施行する群と40Gy（15 fraction）を3週間施行する群とを比較した。データの結果、START Aで平均9.3年間追跡された女性2,236人においては139件の局所腫瘍再発が認められ、平均9.9年間追跡されたSTART Bでは2,215人の女性において95件の局所再発が認められた。10年局所ー領域再発率は、START Aで50Gy照射後は7.4%、41.6Gy照射後は6.3%、39Gy照射後は8.8%であった。3週間15 fractionスケジュールが現在英国における標準治療であり、他の国々においてもますます一般的になりつつある。

Full Text

Appropriately dosed hypofractionated radiotherapy was gentle on healthy tissues and effective in controlling local-regional early breast cancer, according to 10-year follow-up results from the U.K. Standardization of Breast Radiotherapy Trials (START), presented at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium.

"Long-term follow-up confirms that a lower total dose of radiation in fewer, slightly larger fractions delivered over a shorter treatment time is at least as safe and effective as standard five-week schedules of curative radiotherapy in women with early breast cancer," said John Yarnold, M.B.B.S., professor of clinical oncology at The Institute of Cancer Research in London and honorary consultant at The Royal Marsden NHS Foundation Trust.

Between 1999 and 2002, 4,451 women with completely excised invasive breast cancer were recruited to either the START A or START B randomized controlled trials. In START A, researchers compared 50 Gy of postsurgery radiotherapy given in 25 fractions for five weeks versus 41.6 Gy or 39 Gy in 13 fractions for five weeks. In START B, they compared 50 Gy in 25 fractions for five weeks versus 40 Gy in 15 fractions for three weeks.

Data revealed 139 local-regional tumor relapses among the 2,236 women in START A who were followed for an average of 9.3 years and 95 local-regional relapses in the 2,215 women in START B, followed for an average of 9.9 years.

The 10-year local-regional relapse rates for START A were 7.4 percent after 50 Gy, 6.3 percent after 41.6 Gy and 8.8 percent after 39 Gy. In previously published data from START B, the 10-year local-regional relapse rate was 5.5 percent after 50 Gy and 4.3 percent after 40 Gy.

"These long-term data from the START A trial confirm the findings of our earlier results that breast cancer is, on average, as sensitive to the radiation dose of each fraction as the dose-limiting normal tissues of the breast area and that this effect persists for at least 10 years," Yarnold said.

However, a five-week, 13-fraction schedule does not offer shortened overall treatment times. "Hence, we also designed the START B trial, a pragmatic comparison of three-week and standard five-week schedules, testing for noninferiority," said Yarnold. "The 15-fraction schedule is definitely gentler on the healthy tissues, and these long-term data confirm our earlier findings that it appears noninferior in terms of tumor control — a very favorable result."

The three-week, 15-fraction schedule is now the standard of care in the United Kingdom and is becoming increasingly more common in other countries, according to Yarnold. Future research is focused on the molecular mechanisms that determine fraction size sensitivity, which may lead to individualization of fraction size.

"It is likely that some breast cancers are more or less sensitive than others," Yarnold said. "We are also testing a one-week schedule of whole breast radiotherapy against our new three-week standard in the U.K. FAST-Forward Trial."

The START trials were funded by Cancer Research U.K., the U.K. Medical Research Council and the U.K. Department of Health.

TOPICS

乳がんの反応は若年女性においては異なる（Abstract # S3-1）

若年の乳がん女性は高齢の乳がん女性よりも術前補助化学療法への反応が良好である

Young women with breast cancer respond better to neoadjuvant chemotherapy than older women

35歳以下の乳がん女性は高齢女性よりも術前補助化学療法後の病理学的完全寛解に達しやすいとのデータが2012 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、手術可能または局所進行非転移性乳がんに対し術前補助化学療法を施行された女性8,949人を含むドイツの8つのスタディのデータを評価した。彼らは35歳以下の女性704人からなるサブグループの病理学的完全寛解および無病生存率を高齢女性のそれらと比較した。病理学的完全寛解率は非常に若年の女性において有意に高かった（23.6%に対し高齢女性では15.7%）。この差はトリプルネガティブ乳がんおよびルミナル乳がん女性に限られた。腫瘍生物学は病理学的完全寛解や生存率を予測するのに重要な役割を果たすようであった。ルミナルA型がんの女性の無病生存率は病理学的完全寛解ではなく年齢により予測された。しかし、無病生存率が最も不良なのはこのタイプのがんで、病理学的完全寛解に達しなかった35歳未満の女性であった。無病生存率が最も良好だったのは病理学的完全寛解に達した35歳未満の女性であった。

Full Text

Women with breast cancer aged 35 or younger were more likely than older women to achieve a pathological complete response after neoadjuvant chemotherapy, according to data presented at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium.

"Young women with breast cancer are rare, and some data indicate that their prognosis is worse than it is for older women," said Sibylle Loibl, M.D., Ph.D., an associate professor at the University of Frankfurt in Germany. "This is not only because their tumors tend to be more aggressive, but because breast tumors that arise in women who are young seem to be a special biological entity."

Loibl and colleagues evaluated data from eight German studies that included 8,949 women with operable or locally advanced, nonmetastatic breast cancer who were treated with neoadjuvant chemotherapy. The researchers compared pathological complete response and disease-free survival for the subgroup of 704 women aged 35 or younger to those of older women. The subgroup of younger women included a greater proportion of triple-negative breast cancer cases and a smaller proportion of luminal A-type breast cancer cases than in the group of women aged older than 35 (26 percent versus 19 percent and 21 percent versus 27 percent for triple-negative and luminal A-type, respectively).

The pathological complete response rate was significantly higher in very young women — 23.6 percent compared with 15.7 percent among older women. Through further analysis, the researchers found this difference was isolated to women with triple-negative breast cancer and luminal-like breast cancer.

They found no difference in disease-free survival according to age among those patients who achieved a pathological complete response. However, disease-free survival was significantly worse among young women who did not achieve a pathological complete response.

In addition, tumor biology seemed to play an important role, especially in young women, for predicting pathological complete response and survival, according to Loibl. Age, but not pathological complete response, predicted disease-free survival in women with luminal A-type cancer. However, the worst disease-free survival rate was among women with this type of cancer who were younger than 35 and did not achieve a pathological complete response. The best disease-free survival rate was among women younger than 35 who did achieve a pathological complete response.

"The most surprising finding was that young women with a luminal-type tumor — hormone receptor-positive and HER2-negative — who achieved a pathological complete response had a better survival rate than the patients with nonpathological complete response," Loibl said. "This is not true for other age groups, which indicates that breast cancer in the young — even when a luminal-type breast cancer — is chemosensitive."

TOPICS

進行ER陽性乳がんの新たな治療オプション（Abstract # S1-6）

治験薬とレトロゾールの併用は転移性ER陽性乳がんにおいて臨床的有益性を示した

Combination of investigational agent and letrozole demonstrated clinical benefit in metastatic ER-positive breast cancer

治験薬PD 0332991とレトロゾールの併用は進行エストロゲン受容体陽性乳がんの無増悪生存期間中央値を有意に改善したとの第Ⅱ相試験の結果が2012 CTRC-AACRサンアントニオ乳がんシンポジウムで発表された。PD 0332991は、細胞周期進行を阻害することにより細胞DNA合成を阻害する新たな選択的経口サイクリン依存性キナーゼ（CDK）4/6阻害剤である。研究者らは、転移性エストロゲン受容体（ER）陽性乳がんの閉経後女性66人を、PD 0332991とレトロゾールの併用群またはレトロゾール単独群に無作為に割り付けた。無増悪生存期間は併用群で26.1か月であったのに対しレトロゾール単独群では7.5か月であった。測定可能な疾患を有する患者における奏効率は併用群で45%であり、レトロゾール単独群では31%であった。臨床上の有益率は併用治療群で70%であり、レトロゾール単独群で44%であった。サイクリンD1増幅またはp16傷害のバイオマーカーをレトロスペクティブに解析した結果、ER陽性はPD 0332991の有益性を最も受けやすい患者を選択するのに必要な唯一のバイオマーカーであることが明らかにされた。

Full Text

The combination of the investigational agent PD 0332991 and letrozole significantly improved median progression-free survival in patients with advanced estrogen receptor-positive breast cancer, according to phase II results presented at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium.

"We are very encouraged by this improvement in progression-free survival," said Richard S. Finn, M.D., associate professor of medicine at the Jonsson Comprehensive Cancer Center at the University of California, Los Angeles.

PD 0332991, which is being developed by Pfizer Inc., is a novel oral selective inhibitor of cyclin-dependent kinase (CDK) 4/6, which prevents cellular DNA synthesis by blocking cell cycle progression, Finn said. Previously published preclinical data have suggested that CDK 4/6 inhibition may play a role in the treatment of some breast cancers.

In the first part of this two-part, phase Ⅱ study, Finn and colleagues randomly assigned 66 postmenopausal women with metastatic estrogen receptor (ER)-positive breast cancer to either the combination of PD 0332991 and letrozole or to letrozole alone. The second part of the study involved 99 patients with ER-positive cancers determined by screening to have certain genomic alterations, specifically cyclin D1 amplification and/or p16 loss, according to Finn.

Results showed that progression-free survival was 26.1 months for those in the combination arm versus 7.5 months for patients treated with letrozole alone. There was also a 45 percent response rate with the combination treatment versus 31 percent with letrozole alone in patients with measurable disease. The clinical benefit rate was 70 percent with the combination treatment and 44 percent with letrozole alone.

The combination of PD 0332991 and letrozole was also well tolerated. The most common adverse events were neutropenia, leukopenia, anemia and fatigue. "Importantly, this was uncomplicated neutropenia," Finn said. "There was no evidence of febrile neutropenia."

Further, after retrospectively analyzing the biomarkers for cyclin D1 amplification or p16 loss, the researchers found that "ER positivity was the only biomarker we really needed to select patients who were most likely to benefit from PD 0332991," he said.

"If these results are verified in a large, phase III study this could establish PD 0332991 as an important new treatment option for advanced ER-positive breast cancer in a frontline setting."

TOPICS

倦怠感は化学療法に関連した認知機能の問題に影響する(Abstract # S6-3)

乳がん女性においては化学療法前から神経認知問題が存在する可能性がある

Neurocognitive problems may be present before chemotherapy in women with breast cancer

化学療法を施行され認知機能の問題を経験する、一般的に"ケモブレイン"と呼ばれる症状を有する女性は治療開始前から神経認知反応の変化を示すとのデータが2012 CTRC-AACRサンアントニオ乳がんシンポジウムで発表された。研究者らは機能的磁気共鳴画像(fMRI)を用いて、術後補助化学療法を施行された女性28人、放射療法を施行された女性37人および健康なコントロール32人の神経認知反応を検査した。治療前および治療1か月後に参加者は、fMRI画像検査中に様々なレベルの認知制御を必要とする言語作業記憶課題を行った。また、倦怠感に関して自己報告を行った。化学療法を施行された女性は、治療前および治療後1か月に有意に高レベルの倦怠感を訴え認知機能検査の正確性が低かった。さらに、倦怠感が強いほど検査の成績が不良でありスタディ期間中に報告される認知機能の問題が多かった。治療前の脳画像は両治療群においてコントロール群よりも課題を施行するのに必要な領域の機能が低下しており、化学療法を待機している女性においてより多く認められた。放射線療法群の成績は他の2群の成績の中間であった。マインドフルネス介入、心理的サポート、認知行動療法および運動療法などの乳がん診断後のストレスを除去する既存の介入を研究者らは推奨している。

Full Text

Women undergoing chemotherapy who experience cognitive problems, commonly referred to as "chemo brain," displayed alterations in neurocognitive responses prior to undergoing treatment, according to data presented at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium.

Bernadine Cimprich, Ph.D., R.N., associate professor emerita at the University of Michigan School of Nursing in Ann Arbor, and colleagues found that pretreatment neurocognitive compromise and fatigue were key contributors to the cognitive effects often attributed to chemotherapy.

"For a long time, women undergoing treatment for breast cancer have reported cognitive problems such as trouble thinking clearly, remembering things, and carrying out jobs and other responsibilities, which we have attributed to chemotherapy or 'chemo brain,'" Cimprich said. "Research shows that these problems do occur in some women during chemotherapy, but we still do not understand what the underlying causes are."

Cimprich and her colleagues reasoned that the mental demand and stress of a breast cancer diagnosis could play a role in these early cognitive problems. They tested neurocognitive responses using functional magnetic resonance imaging (fMRI) on 28 women who received adjuvant chemotherapy, 37 who received radiotherapy and 32 healthy controls. Before treatment and one month after treatment, the participants performed a verbal working memory task with varying levels of demand for cognitive control during fMRI scanning. They also provided self-reports of fatigue.

Women who underwent chemotherapy reported a significantly higher level of fatigue and performed less accurately on the cognitive tests before treatment and one month after treatment. In addition, greater fatigue correlated with poorer test performance and more cognitive problems reported over time.

Brain imaging before treatment showed reduced function in regions needed to perform the task in both patient groups when compared with controls, with more compromise seen in women awaiting chemotherapy. Women who were less successful in recruiting the brain regions needed for the task before treatment were more likely to suffer greater fatigue over time, regardless of treatment group. "Our initial findings showed that the level of worry interfered with patients' ability to do a task," Cimprich said. "The level of worry had a key role in the cognitive problems with these women before treatment, and this worry was related to fatigue."

Scores for cognitive testing from women who underwent radiation treatment fell between those of women who underwent chemotherapy and those of the healthy women.

"Women faced with the decision to undergo chemotherapy should know that cognitive problems, should they occur, may not always stem from chemotherapy," Cimprich said. "Women should not avoid accepting recommendations for lifesaving chemotherapy for fear of 'chemo brain.'"

Cimprich recommended existing interventions to combat stress after a breast cancer diagnosis, including mindfulness intervention, psychological support, cognitive behavior interventions and exercise.

"It might be possible to diminish worry and fatigue and maintain strong brain function during the course of treatment using these interventions," Cimprich said.
The research was funded by the National Institutes of Health.

TOPICS