前立腺がんに対する初めての有効な術後補助化学療法 (Abstract LBA5002)

標準治療にドセタキセルを追加することにより高リスク局所前立腺がんの生存率が改善する

Adding docetaxel to standard care improves survival for men with high-risk, localized prostate cancer

標準的なホルモン療法および放射線療法にドセタキセルを追加することにより高リスク局所前立腺がん患者の死亡リスクが軽減する、と第51回American Society of Clinical Oncology年次集会で発表された。この第III相スタディにおいて、高リスク局所進行前立腺がん患者562人が標準治療（放射線療法と2年間のホルモン療法の併用）または標準治療後にドセタキセル化学療法を受ける群にランダムに割り付けられた。ドセタキセルは放射線療法終了後1か月から始まり、18週間投与された。平均追跡期間5.5年の後に標準治療群では52人が死亡し、ドセタキセル群では36人であった。4年全生存率は標準治療群で89%であり、ドセタキセル群では93%であった。ドセタキセルはまた、再発リスクも低下させた—5年無病生存率は標準治療群で66%であり、ドセタキセル群では73%であった。今回のスタディは局所前立腺がんの術後補助化学療法において化学療法が役目を果たすことを示した初めてのものであり、時間と共に多大な生存率への有益性を認めるであろう、と筆者らは述べている。

Full Text

A phase III study found that adding docetaxel chemotherapy to standard hormone and radiation therapy reduces the risk of death for men with high-risk, localized prostate cancer according to researchers at the American Society of Clinical Oncology's 51st Annual Meeting. At an average follow-up of 5.5 years, four-year overall survival rates were 89% in the standard therapy group vs. 93% in the docetaxel group.

"This study is the first indication that chemotherapy has a role in the adjuvant treatment of localized prostate cancer, and we also expect to see an even bigger survival advantage over time," said lead study author Howard Sandler, M.D., a professor of radiation oncology at the Cedars-Sinai Medical Center in Los Angeles, CA. "This finding could improve outcomes for thousands of men. At the same time, chemotherapy carries a modest increase in side effects, so it is important that physicians discuss the balance of benefits and risks with their patients."

The goal of adjuvant therapy is to lower the risk of recurrence and improve overall survival. Among the most common cancers – lung, breast, colorectal, and prostate – prostate cancer is the only disease without an established adjuvant chemotherapy regimen.

In the study, 562 men with high-risk, locally advanced prostate cancer were randomly assigned to treatment with standard therapy (radiation therapy plus two years of hormone therapy) or standard therapy followed with docetaxel chemotherapy. Docetaxel was given for 18 weeks, starting a month after radiation therapy.

After an average follow-up period of 5.5 years, 52 deaths occurred in the standard therapy group compared to only 36 deaths in the docetaxel group. The four-year overall survival rates were 89% in the standard therapy group compared to 93% in the docetaxel group. Docetaxel also reduced the risk of relapse — the five-year disease-free survival rates were 66% in the standard therapy group vs. 73% in the docetaxel group.

Patient follow-up will continue to determine the long-term benefit of adjuvant chemotherapy in this setting, and an analysis of quality of life data will be performed at a later time.

"Adjuvant chemotherapy has delivered major survival gains to people with several of the most common types of cancer, and now we're finally seeing the same with prostate cancer," said ASCO Expert Charles J. Ryan, M.D.. "Here we have a powerful new use for a long-established therapy. It's an advance that would not have been possible without federally funded clinical trials."

This study received funding from The National Institutes of Health, Sanofi, and AstraZeneca.

ASCO2015特集

免疫療法はほとんどの一般的な肺がんにおいて生存期間を延長する (Abstract LBA109)

Nivolumabは非扁平上皮非小細胞肺がんに対する標準的なセカンドライン治療選択となり得る

Nivolumab as a possible standard second-line treatment option for non-squamous non-small cell lung cancer

第51回American Society of Clinical Oncology年次集会で発表された研究の結果、非扁平上皮、非小細胞肺がん（NSCLC）患者に対し、PD-1免疫療法は有効な治療であることが示された。プラチナ製剤ベースの化学療法後に悪化した進行肺がん患者において、nivolumab治療を受けた患者の生存期間はドセタキセルで治療された患者よりも3か月長かった。この第III相スタディでは進行非扁平上皮NSCLC患者582人をnivolumabまたはドセタキセルで治療する群にランダムに割り付けた。奏効率はnivolumab群においてドセタキセル群よりも高かった（19.2%対12.4%）。またnivolumab群において有意に長い持続的な奏効が得られた（平均17.1か月対5.6か月）。全生存期間中央値はnivolumab群で12.2か月であり、ドセタキセル群では9.4か月であった。特筆すべきことに、腫瘍内PD-L1が高レベル（≥1%細胞）のサブグループにおいては、nivolumab治療群の生存期間中央値は17か月を超えたのに対しドセタキセル群では9か月であった。Nivolumabの忍容性は全般的に良好であった。Nivolumabは治療歴のあるNSCLC患者の新たな標準治療となり得る、と研究者らは述べている。

Full Text

Findings from a phase III study presented at the American Society of Clinical Oncology's 51st Annual Meeting indicate that PD-1 immunotherapy is an effective treatment option for patients with non-squamous, non-small cell lung cancer (NSCLC). Among patients with advanced disease that worsened after receiving platinum-based chemotherapy, those treated with nivolumab lived on average three months longer than those treated with docetaxel chemotherapy.

"This is the first phase III study to show that immunotherapy is effective against non-squamous cell NSCLC, and appears to be particularly active in patients with PD-L1-positive tumors," said lead study author Luis Paz-Ares, M.D., Ph.D., a professor of medicine at Hospital Universitario 12 de Octubre in Madrid, Spain. "While nivolumab appears to be more potent against this most common lung cancer, it is important to note that it is also far easier on patients compared to the standard second-line treatment, docetaxel."

Lung cancer is the most common cancer worldwide, with more than 1.8 million new cases diagnosed in 2012. NSCLC is the most common form of lung cancer, accounting for 85% of all lung cancers. More than two-thirds of those are non-squamous cell cancers.

The study randomly assigned 582 patients with advanced non-squamous NSCLC to treatment with nivolumab or docetaxel. Response rates were higher in the nivolumab group compared to the docetaxel group (19.2% vs. 12.4%). Responses also lasted significantly longer in the nivolumab group (17.1 months vs. 5.6 months, on average).

The median overall survival was 12.2 months in the nivolumab group compared to 9.4 months in the docetaxel group. Of note, in the subgroup of patients with high levels of PD-L1 in their tumor (≥1% cells), the median survival with nivolumab exceeded 17 months as compared to 9 months for those treated with docetaxel.

Nivolumab was well tolerated overall, with only one in 10 patients experiencing serious side effects, compared to more than half of patients in the docetaxel arm. There was one treatment-related death in the docetaxel arm and none in the nivolumab arm. Due to toxic side effects, 4.9% patients stopped nivolumab, and 14.9% patients stopped docetaxel.

Nearly half of the patients who stopped treatment subsequently received systemic therapy.

The researchers pointed out that patients with higher levels of the biomarker PD-L1 experienced the greatest degree of benefit from nivolumab. Overall, patients who received nivolumab had a 27% lower risk of death compared to those who received docetaxel. However, the subgroup of patients with the high levels of PD-L1 had a 41- 60% reduction in risk of death, which was not observed in cases of low or undetectable PD- L1 levels.

Dr. Paz-Ares stated that nivolumab could potentially become a new standard therapy for patients with previously treated NSCLC.

ASCO Expert Gregory A. Masters, MD, FACP, FASCO noted that "Even five years ago, an effective immunotherapy for lung cancer was largely considered impossible. Today, we have such a treatment, and it surpasses the standard therapy both in terms of efficacy and patient quality of life."

This study received funding from Bristol-Myers Squibb.

ASCO2015特集

一部のがんにおいてゲノム異常は抗PD-1反応の予測因子となる (Abstract LBA100)

いくつかのタイプのがん患者において特定のゲノム異常によりpembrolizumabの有効性が予測できる

Specific genomic abnormality predicts response to pembrolizumab in patients with several types of cancer

第51回American Society of Clinical Oncology年次集会で発表された第II相試験において初めてのゲノムマーカーーミスマッチ修復（MMR）欠損ーにより広範ながんに対する抗PD-1抗体pembrolizumabの有効性が予測できることが示された。スタディには3群の患者ーMMR正常転移性大腸がん（CRC 25人）、MMR欠損転移性CRC(13人)、および他のMMR欠損がん（10人）ーが含まれた。全ての患者が過去の治療にもかかわらず悪化した進行性転移性がんを有していた。奏効率はMMR欠損CRCとMMR正常CRCとで大きく異なった（62%対0%）一方で、病勢コントロール率（腫瘍縮小または増殖抑制）の差はより大であったーMMR欠損群の92%に対しMMR 正常群では16%であった。有効性を示す血液マーカー変化は治療開始後数週間以内に認められ、患者はほぼ治療直後に体調が改善した。他のMMR欠損がん群（CRCsを除く）における全奏効率は60%であった。奏効は、進行子宮内膜がんおよび乳頭部、十二指腸、胆のうがん、および胃がんなどのいくつかのタイプの進行消化器がんにおいて認められた。最後の解析において、奏効は1人の患者以外においては継続中であり多くは1年以上持続していた。

Full Text

A phase II study presented by researchers at the American Society of Clinical Oncology's 51st Annual Meeting identified the first genomic marker – mismatch repair (MMR) deficiency – to predict response to the anti-PD-1 antibody pembrolizumab. This marker predicted responses across a range of cancers.

Among patients with colorectal cancer (CRC), 62% of those with MMR-deficient tumors experienced tumor shrinkage, while no responses were detected among those without this abnormality ("MMR-proficient"). The response rate among patients with other MMR-deficient cancers was similar – 60%.

MMR deficiency is found in 15-20% of sporadic (non-inherited) CRCs and in nearly all CRCs associated with Lynch syndrome, which constitute up to 5% of all CRCs. MMR deficiency is also found in other tumor types including stomach, small bowel, endometrial, prostate, and ovarian cancer.

Testing for MMR-deficiency is widely available and may enable doctors to identify a larger population of patients who might benefit from pembrolizumab and other PD-1 drugs.

"This study is really about bridging immunotherapy and genomics for the benefit of patients, and it has implications for a broad range of cancers," said lead study author Dung T. Le, MD, an assistant professor of oncology at Johns Hopkins Kimmel Cancer Center in Baltimore, M.D.. "Opening the door to this effective new therapy would be a breakthrough for this subset of patients with metastatic colon cancer and other hard-to-treat cancers."

MMR deficiency leads to an accumulation of genetic mutations in a tumor. "When you have a tumor that has thousands of mutations, this increases the probability that the immune system can recognize and destroy the tumor. So, we suspected that immune checkpoint inhibitors such as pembrolizumab would work particularly well against MMR-deficient tumors," added Dr. Le.

In this study, MMR-deficient tumors had an average of 1,782 mutations, compared to 73 mutations in MMR-proficient tumors. Higher numbers of mutations were linked to better response to pembrolizumab.

The study included three groups of patients: MMR-proficient metastatic CRC (25 patients), MMR-deficient metastatic CRC (13 patients), and other MMR-deficient cancers (10 patients). All patients had progressive metastatic cancer that had worsened despite prior treatment.

While researchers observed a large difference in response rates between MMR-deficient and -proficient CRCs (62 vs. 0%), the difference in disease control rates (tumor shrinkage or suppressed growth) was even greater – 92% in the MMR-deficient group and only 16% in the MMR-proficient group. Blood marker changes such as CEA levels indicating response were seen within the first few weeks of starting treatment, and patients tended to feel better almost immediately.

In the group of other MMR-deficient cancers (excluding CRCs), the overall response rate was 60%. Responses were detected in patients with advanced endometrial cancer and several types of advanced gastrointestinal cancers including ampullary, duodenal, cholangiocarcinoma, and gastric cancers. Few treatment options exist for such patients. At last analysis, responses were ongoing for all but one patient, and many responses have lasted for over a year.

Dr. Le indicated that the next step is to reproduce the findings of this prospective study in a larger group of patients to solidify the observation that MMR deficiency is a predictor of response to therapies targeting PD-1. She noted that the durability of response with little toxicity could eventually lead to testing this approach in initial treatment for these patients.

Pembrolizumab is currently only FDA approved to treat patients with advanced melanoma that has not responded to other standard therapies. Another PD-1 therapy, nivolumab, is approved for the same indication, as well as in advanced squamous lung cancer.

"This study helped identify a whole new population of patients who might benefit from PD-1 immunotherapy. MMR deficiency appears to be a predictor of response to nivolumab, and it's very encouraging that the responses in MMR-deficient tumors thus far have been long-lasting," said ASCO Expert Smitha S. Krishnamurthi, M.D..

This study received funding from Swim Across America, The Commonwealth Fund, The Ludwig Center at Johns Hopkins, and the National Institutes of Health.

ASCO2015特集

再発CLLの予後改善 (Abstract LBA7005)

新たなibrutinib併用療法は再発慢性リンパ性白血病においてかなりの恩恵をもたらす

New ibrutinib combination regimen shows substantial benefits in relapsed chronic lymphocytic leukemia

Ibrutinibとベンダムスチン+リツキシマブ（BR）の併用は過去の治療にもかかわらず悪化した慢性リンパ性白血病（CLL）患者の予後を改善するとの大規模第III相試験の中間解析結果が第51回American Society of Clinical Oncology年次集会で発表された。このスタディにおいて治療歴のあるCLL患者578人がibrutinibとBRまたはプラセボとBRで治療される群にランダムに割り付けられた。平均17.2か月の追跡期間の後、無増悪期間中央値はプラセボ群で13.3か月でありibrutinib群では期間中央値には達しなかった。進行または死亡のリスクはibrutinib投与群で80%低下した。奏効率はibrutinib群においてプラセボ群より有意に高かった（82.7%対67.8%）。疾患関連の倦怠感はibrutinib群で改善し、患者はその効果を早期に報告した（6か月後対14か月後）。副作用発現率と種類は2群間で同等であった。今回の顕著な結果に基づき、プラセボ群患者はibrutinib投与群にクロスオーバーすることが許可された。中間解析の時点で、プラセボ群患者の90人（31%）の患者がibrutinib群にクロスオーバーした。

Full Text

The combination of ibrutinib and bendamustine/rituximab (BR) improves outcomes for patients with chronic-lymphocytic leukemia (CLL) that worsened despite prior therapy according to an interim analysis of a large phase III study presented at the American Society of Clinical Oncology's 51st Annual Meeting.

At a median follow-up of 17 months, patients who received ibrutinib and BR had an 80% lower risk of disease progression or death than those who received placebo and BR. Based on this striking benefit, patients were permitted to cross over from the placebo group to receive ibrutinib.

For years, the standard treatment for CLL has been a combination of chemotherapy and targeted therapy (e.g., rituximab). Although these treatments help control the disease for many years, they cannot cure it, and all patients ultimately become resistant to therapy.

Until recently, patients whose disease worsened or came back despite treatment have had limited options. Last year, however, the FDA approved two new targeted drugs for such patients ─ ibrutinib and idelalisib in combination with rituximab. Ibrutinib is a first-in-class oral once-daily targeted treatment that blocks Bruton's tyrosine kinase (BTK). This protein fuels the growth of lymphocytes, the type of white blood cells that are affected by CLL.

"This was one of the most rigorous clinical trials ever conducted in CLL and it truly validates ibrutinib as an important drug for this cancer," said lead study author Asher Chanan-Khan, M.D., a professor of medicine at Mayo Clinic in Jacksonville, FL. "We found that ibrutinib can be safely paired with existing therapy to powerfully prolong remissions and improve patients' well-being."

In the study, 578 patients with previously treated CLL were randomly assigned to treatment with ibrutinib and BR or placebo and BR. After an average follow-up of 17.2 months, the median progression-free survival was 13.3 months in the placebo group and was not reached in the ibrutinib group. The risk of progression or death was decreased by 80% in those who received ibrutinib.

Response rates were significantly higher in the ibrutinib group than in the placebo group (82.7% vs. 67.8%). Disease-related fatigue improved in the ibrutinib group, and patients reported benefit sooner (at six months vs. 14 months).

At the time of the interim analysis, 90 (31%) patients from the placebo group had already crossed over to the ibrutinib group. The rates and types of side effects were comparable between the two treatment groups. The most frequent side effects were low blood cell counts and nausea.

The next steps for this area of research include evaluating ibrutinib as a single agent and in combination with drugs targeting the CD20 protein in patients with newly diagnosed, symptomatic, and asymptomatic CLL.

"Progress against chronic lymphocytic leukemia was one of the most important themes of the last two years, and now we have yet another potent treatment approach for patients who have exhausted other options," said ASCO Expert Merry-Jennifer Markham, M.D.. "These results suggest that we can achieve better outcomes for patients by pairing novel therapies with established treatments."

This study received funding from Janssen Research & Development, LLC (Janssen).

ASCO2015特集

ビタミンB3による化学予防 (Abstract 9000)

ONTRAC：ニコチン酸アミドの経口摂取は高リスクの人々における非メラノーマ皮膚がん発症率を低下させる

ONTRAC: Oral nicotinamide reduces rates of non-melanoma skin cancer in people at high risk of the disease

ONTRAC（Australian Oral Nicotinamide to Reduce Actinic Cancer）スタディの結果、ニコチン酸アミドと呼ばれるビタミンB3の一種は高リスクの人々における新たな皮膚がんを有意に軽減させる、と第51回American Society of Clinical Oncology年次集会で発表された。このスタディにおいて、過去5年間に少なくとも2つの非メラノーマ皮膚がんを発症し、したがって高リスクと考えられた患者386人がニコチン酸アミドまたはプラセボを12か月間毎日内服する群にランダムに割り付けられた。スタディ対象は皮膚がんクリニックで一般的に見られる患者の混成割合を反映していた（平均年齢66歳、男性が3分の2）。新たに非メラノーマ皮膚がんと診断された率はニコチン酸アミド群においてプラセボ群よりも23%低かった。治療開始後3か月後に日光角化症例数はニコチン酸アミド群で11%減少し、9か月後には20%減少した。ニコチン酸アミドの予防効果は基底細胞がんと扁平上皮細胞がんとで同等であった。ビタミンB3の一種であるニコチン酸アミドは副作用を引き起こすことで知られているが、今回のスタディにおいてニコチン酸アミドは重症の副作用は何も来さなかった。

Full Text

The Australian Oral Nicotinamide to Reduce Actinic Cancer (ONTRAC) Study shows that a form of vitamin B3 called nicotinamide significantly reduces rates of new skin cancers in people at high risk of the disease. Taken as a twice-daily pill, nicotinamide reduced the incidence of new non-melanoma skin cancers by 23%.
The results of ONTRAC were presented at the American Society of Clinical Oncology's 51st Annual Meeting.

Nicotinamide is safe, affordable, and available over the counter in most countries. The findings have the potential to decrease the health burden and economic cost of skin cancer – the most common form of cancer in fair-skinned populations worldwide.

"This is the first clear evidence that we can reduce skin cancers using a simple vitamin, together with sensible sun protection. We hope that these findings can be immediately translated into clinical practice," said senior study author Diona Damian, MBBS, Ph.D., a professor of dermatology at the Dermatology University of Sydney. "However, people at high risk of skin cancer will still need regular check-ups with their doctor."

The primary cause of non-melanoma skin cancer is sun exposure. Despite intensive sun protection campaigns, the incidence of skin cancer is continuing to increase worldwide.

In this study, 386 patients who had at least two non-melanoma skin cancers in the last five years – and were therefore considered to be at high risk – were randomly assigned to daily nicotinamide or placebo for 12 months. The study population reflected the mix of patients typically seen in a skin cancer clinic – the average age was 66 years, and two-thirds of the patients were men (skin cancer is more common in men). Many of the patients had ongoing medical issues, such as heart disease, arthritis, high blood pressure, and chronic lung disease.

The rates of new non-melanoma skin cancer diagnoses were 23% lower in the nicotinamide group compared to the placebo group. The numbers of actinic keratoses were reduced in the nicotinamide group by 11% at three months, and by 20% at nine months of treatment. Whilst nicotinic acid, which is a different form of vitamin B3, is known to cause side effects including headaches, flushing, and low blood pressure, nicotinamide lacks these side effects and was not associated with any serious side effects in the study.

The most common types of non-melanoma skin cancer are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). SCCs can spread to lymph nodes and internal organs. BCCs rarely spread but can cause cosmetic problems as they often occur on the face. Nicotinamide had comparable efficacy in preventing BCC and SCC.

UV radiation in sunlight causes skin cancer via two key pathways – DNA damage and suppression of skin immunity. This study builds on a decade of preclinical and early clinical studies, which suggested that nicotinamide both enhances the repair of DNA in skin cells damaged by sunlight, and protects the skin's immune system against UV light.

DNA repair is an energy-intensive process. UV radiation actively blocks energy production in skin cells. Cells convert nicotinamide into a molecule called nicotinamide adenine dinucleotide, which is essential for cellular energy production. The researchers believe that nicotinamide thus helps replenish cellular energy after sunlight exposure, giving cells the energy boost they need to repair DNA damage and prevent immune suppression.

Further studies are planned to determine if nicotinamide can help reduce skin cancers in people with suppressed immune systems, such as organ transplant recipients who have to take lifelong immune suppressive medications. People with suppressed immune systems have skin cancer rates up to 50 times higher than those with normal immune systems.

"Every opportunity to prevent cancer is welcome news" commented ASCO President Peter Paul Yu, M.D., FACP, FASCO. "With this study, we have a remarkably simple and inexpensive way to help people avoid repeat diagnoses of some of the most common skin cancers. With just a daily vitamin pill, along with sun protection and regular skin cancer screenings, people at high risk for these types of skin cancers have a good preventive plan to follow."

This study received funding from Australia's National Health and Medical Research Council (NHMRC).

ASCO2015特集

再発多発性骨髄腫に対する新たな免疫療法の選択肢 (Abstract 8508)

ELOQUENT-2：Elotuzumabを追加することにより再発多発性骨髄腫進行のリスクが有意に低下する

ELOQUENT-2: Adding elotuzumab significantly reduces risk of progression for relapsed multiple myeloma

第51回American Society of Clinical Oncology年次集会で発表された第III相試験の中間結果により、革新的な免疫療法が再発多発性骨髄腫の新たな治療選択肢になる可能性のあることが示唆された。このスタディにおいて、再発多発性骨髄腫の患者646人がレナリドミドとデキサメタゾン（コントロール群）またはレナリドミドとデキサメタゾンに加えelotuzumabを投与する群にランダムに割り付けられた。追跡期間中央値24か月後に、elotuzumabはがん進行および死亡のリスクを30%低下させた。Elotuzumab群患者の疾患無増悪期間（平均19.4か月）はコントロール群（平均14.9か月）よりも有意に長かった。さらに、高リスク所見—del(17p)およびt[4;14]と呼ばれる遺伝子異常—を有する二つのサブグループは、平均リスク患者と同等にelotuzumabの恩恵を被るようであった。これらのハイリスク患者においては従来の治療法は有効性が低い傾向にある。概して、elotuzumabの忍容性は良好で、患者のQOLを低下させたり症状による負荷を増強したりすることはなかった。これは多発性骨髄腫におけるモノクローナル抗体を調査した最大のスタディであり、この疾患の治療として標的免疫療法を用いた際の有益性を示した初めての第III相試験である。

Full Text

Interim results of a phase III trial presented at the American Society of Clinical Oncology's 51st Annual Meeting suggest an innovative immune-based therapy may offer a new option for patients with relapsed multiple myeloma. The new monoclonal antibody elotuzumab, added to standard lenalidomide and dexamethasone therapy, extended the duration of remissions by about five months, on average, compared to standard treatment alone.

"It appears that, for patients with relapsed multiple myeloma who would otherwise be offered lenalidomide and dexamethasone, addition of this new targeted drug makes the outcomes even better," said lead study author Sagar Lonial, M.D., Chief Medical Officer of the Winship Cancer Institute of Emory University, and professor and executive vice chair of the Department of Hematology and Medical Oncology of Emory University School of Medicine in Atlanta, Ga. "It was particularly striking that the difference between the elotuzumab and control groups seems to get bigger over time, which really speaks to the power of this immune-based approach."

Elotuzumab attaches to a cell surface protein called SLAMF7, which is found on myeloma cells and on a type of immune cells known as natural killer (NK) cells. Scientists believe that elotuzumab mounts a two-pronged attack on cancer by targeting myeloma cells directly and by enhancing the NK cells' ability to kill myeloma cells.

Currently, there are no monoclonal antibodies approved for treatment of multiple myeloma. This is the largest study of a monoclonal antibody in multiple myeloma and the first phase III trial demonstrating benefit using a targeted immune-based approach to treating the disease.

In the study, 646 patients with recurrent multiple myeloma were randomly assigned to receive lenalidomide and dexamethasone (control group) or lenalidomide and dexamethasone with elotuzumab.

At a median follow-up period of 24 months, elotuzumab reduced the risk of cancer progression and death by 30%. Patients in the elotuzumab group experienced a significantly longer period without disease progression (19.4 months, on average) than those in the control group (14.9 months, on average). In addition, two subgroups of patients with high-risk features — genetic abnormalities termed del(17p) and t[4;14] — appeared to benefit from elotuzumab as much as patients with average risk. Conventional therapies tend to be less effective in those high-risk patients.

Overall, elotuzumab was well tolerated and did not deteriorate patient's quality of life or exacerbate symptom burden. Mild infusion reactions occurred after the first few doses in 10% of patients in the elotuzumab arm.

Ongoing clinical trials are exploring the possibility of incorporating elotuzumab into therapies for patients with newly diagnosed multiple myeloma and testing various combinations of elotuzumab and existing treatments.

"We've made much headway over the past decade in understanding and treating multiple myeloma, the third most common blood cancer," noted ASCO President-Elect Julie M. Vose, M.D., MBA, FASCO. "This study is an innovative approach – one that combines the precision of a targeted, immune-based therapy with traditional myeloma therapy. The results are very encouraging, giving renewed hope to patients who have relapsed."

This study was funded by Bristol-Myers Squibb and AbbVie.

ASCO2015特集

治療によりメラノーマの進行が半減する (Abstract LBA1)

進行メラノーマにおいて初回のニボルマブベースの治療は疾患進行までの時間を2倍以上にする

Initial nivolumab-based treatment more than doubles time to disease progression in advanced melanoma

未治療の進行メラノーマ患者におけるニボルマブ単独またはイピリムマブとの併用による初回治療は、イピリムマブ単独治療よりも有効性が高い、と第51回American Society of Clinical Oncology年次集会で発表された。第III相スタディでは、945人の患者をイピリムマブ、ニボルマブ、またはこれら2剤の併用にランダムに割り付けた。少なくとも9か月の追跡期間後に、疾患進行までの平均期間はニボルマブ単独群においてイピリムマブ群の倍であり(8.9か月対2.2か月)、この有益性はイピリムマブとニボルマブを併用することでさらに増大した(11.5か月)。奏効率もまた、併用療法群(57.6%)およびニボルマブ単独群(43.7%)において、イピリムマブ群(19%)よりも実質的に高かった。腫瘍量の平均軽減率は併用療法群で51.9%であり、ニボルマブ単独群で34.5%であった。対照的に、イピリムマブ単独投与患者では腫瘍量が5.9%増大した。予想通り、重篤な薬剤性副作用の発現率は併用群(55%)において最も高く、この群の36%の患者が治療を中止しなければならなかった。先行研究では、免疫療法を早期に中止した多くの患者が依然として経過が良好であることが示されている、と筆者らは述べている。

Full Text

A randomized phase III trial indicates that initial therapy with nivolumab alone or in combination with ipilimumab is significantly more effective than ipilimumab alone in patients with previously untreated advanced melanoma according to researchers at the American Society of Clinical Oncology's 51st Annual Meeting.

Nivolumab alone more than doubled the average time to disease progression, compared to ipilimumab (8.9 months vs. 2.2 months), and the benefit was even greater when ipilimumab and nivolumab were combined (11.5 months). The response rates were also substantially higher in patients receiving the combination therapy (57.6%) and nivolumab (43.7%) alone, as compared to ipilimumab (19%).

"We're very encouraged that the initial observations about the efficacy of this combination held up in this large phase III trial," said lead study author Jedd Wolchok, MD, PhD, Chief of Melanoma and Immunotherapeutics Service at Memorial Sloan Kettering Cancer Center in New York, NY. "Our study also suggests that patients with a specific tumor marker appear to benefit the most from the combination treatment, whereas other patients may do just as well with nivolumab alone. This will help doctors provide important insight for patients on which treatment is right for them."

Nivolumab and ipilimumab are monoclonal antibodies that block two different immune checkpoints – PD-1 and CTLA-4, respectively. Both treatments, commonly referred to as checkpoint inhibitors, essentially boost the immune system's ability to fight cancer.

Prior research has shown that immune checkpoint inhibitors can improve survival for patients with melanoma and lung cancer.

This study randomly assigned 945 patients with previously untreated, advanced melanoma to receive ipilimumab, nivolumab, or the combination of the two. After a follow-up period of at least nine months, the median progression-free survival was 2.2 months for ipilimumab, 8.9 months for nivolumab, and 11.5 months for the combination. The differences between the combination and ipilimumab groups, and nivolumab and ipilimumab groups were statistically significant (both comparisons p=0.001).

The response rates for the combination, nivolumab, and ipilimumab groups were 57.6%, 43.7%, and 19%, respectively. The average reductions in tumor burden were 51.9% with the combination and 34.5% with nivolumab alone. In contrast, patients who received ipilimumab alone experienced a 5.9% increase in tumor burden.

As expected, the rate of serious drug-related side effects was the highest in the combination group (55%), and 36% of patients in this group had to stop the therapy due to side effects. Dr. Wolchok remarked that prior studies have shown that many patients who stop immunotherapy early still continue to do well.

This prolonged benefit is explained by the fact that immunotherapy works by activating the immune system rather than targeting the tumor directly. It is not yet clear how long patients need to be treated to fully activate the immune system, and the minimal duration of therapy probably varies from patient to patient.

Quality of life data were collected on the study, and the analysis of those results will be reported at a later time.

The PD-1 protein on immune cells attaches to another protein called PD-L1, which is sometimes found on the surface of some tumor cells. Prior research suggested that patients who had detectable PD-L1 levels in their tumor (PD-L1-positive tumors) typically had better responses to PD-1 therapy.

In this study, nivolumab alone seemed to be as effective against PD-L1-positive tumors as the combination of nivolumab and ipilimumab. For patients with PD-L1-negative tumors, however, the combination treatment was significantly more beneficial than nivolumab alone.

"Immunotherapy drugs have already revolutionized melanoma treatment, and now we're seeing how they might be even more powerful when they're combined," noted ASCO Expert Steven O'Day, MD. "But the results also warrant caution – the nivolumab and ipilimumab combination used in this study came with greater side effects, which might offset its benefits for some patients. Physicians and patients will need to weigh these considerations carefully."

This study received funding from Bristol-Myers Squibb.

ASCO2015特集

DCISに対する他の良い治療選択肢 (Abstract LBA500)

閉経後DCIS患者においてアナストロゾールを使用した方がタモキシフェンよりも無再発率が高い

Anastrazole offers higher breast cancer-free survival rates than tamoxifen in postmenopausal women with DCIS

第51回American Society of Clinical Oncology年次集会で発表された第III相試験の結果、閉経後DCIS（非浸潤性乳管がん）には乳がん予防の他の選択肢がある可能性が示された。スタディでは、DCIS生存者3,000人あまりにおいて標準的な5年間のタモキシフェン治療と5年間のアロマターゼ阻害剤アナストロゾール治療とを比較した。スタディでは、閉経後ホルモン受容体陽性DCIS患者3,104人がタモキシフェンまたはアナストロゾールを毎日5年間内服する群にランダムに割り付けられた。ホルモン療法開始前に全員が腫瘍摘出術および放射線療法を受けた。平均追跡期間8.6年後に乳がんが検出されたのは、タモキシフェン群で114人であったのに対しアナストロゾール群では84人であった。これには、同側または対側の新たな乳がん発症（DCISまたは浸潤性がん）に加え、DCIS再発が含まれた。10年乳がん無再発率はアナストロゾール群においてタモキシフェン群よりも高く（93.5%対89.2%）、この差は統計学的に有意であった。乳がんによる死亡はタモキシフェン群で8人であり、アナストロゾール群で5人であった。サブグループ解析では、60歳を超える女性においてはアナストロゾールはタモキシフェンより優れてはいない可能性が示された。

Full Text

A federally funded phase III trial presented at the American Society of Clinical Oncology's 51st Annual Meeting suggests that postmenopausal women with ductal carcinoma in situ (DCIS) may have an additional option for breast cancer prevention. The study compared the standard five-year treatment of tamoxifen to five years of the aromatase inhibitor anastrazole in more than 3,000 DCIS survivors. The 10-year breast cancer-free survival rates were higher in the anastrazole group than in the tamoxifen group (93.5% vs. 89.2%).

"The good news is tamoxifen and anastrazole are both very effective, but it seems that women have better chances of staying well with anastrazole," said lead study author Richard G. Margolese, MD, a professor of surgical oncology at The Jewish General Hospital, McGill University in Montreal, Canada. "Women should also consider differences in side effects when discussing treatment options with their doctors."

Women with DCIS are at increased risk of developing invasive breast cancer, although breast cancer-related death is uncommon following DCIS treated with radiation and lumpectomy.

While both tamoxifen and aromatase inhibitors have been used to prevent recurrences of more advanced forms of breast cancer, this is the first study to compare the two treatments in women with DCIS. In the study, 3,104 postmenopausal patients with hormone receptor-positive DCIS were randomly assigned to daily tamoxifen or anastrazole, each given for five years. Prior to starting hormone therapy, all had undergone lumpectomy and radiation therapy.

After an average follow-up period of 8.6 years, 114 breast cancers were detected in the tamoxifen group compared to 84 in the anastrazole group. This included recurrences of DCIS as well as development of a new breast cancer (DCIS or invasive) in the same or other breast. The 10-year breast cancer-free rates were higher in the anastrazole group than in the tamoxifen group (93.5% vs. 89.2%), and this difference was statistically significant.

There were eight deaths due to breast cancer in the tamoxifen group and five in the anastrazole group. While the 10-year overall survival rates were comparable in the two groups (92.5% for anastrazole and 92.1% for tamoxifen), a subgroup analysis revealed that anastrazole may not be superior to tamoxifen in women older than 60 years.

Hormone receptor-positive breast cancer is dependent on estrogen for growth. Tamoxifen and anastrazole block the estrogen growth signal in different ways. While tamoxifen blocks the estrogen receptor, anastrazole suppresses the manufacturing of estrogen.

Generally, there were no significant differences in the toxicity profiles of these agents. The main side effect of anastrazole is hastening of osteoporosis, which increases the risk of bone fracture. Indeed, anastrazole resulted in a higher rate of bone fractures compared to tamoxifen, though the difference was not statistically significant. In addition, treatment with tamoxifen was associated with higher rates of uterine cancer, though the difference also did not reach statistical significance.

ASCO expert Don S. Dizon, MD commented on the study. "Women with DCIS already have several great treatment options, and now they have one more. Aromatase inhibitors offer important advantages, but patients and their doctors should still consider the full range of options, including tamoxifen or even foregoing adjuvant treatment, as every approach carries its own risks and benefits."

This study received funding from the National Institutes of Health.

ASCO2015特集

メラノーマ患者においてリンパ節全郭清は生存率を改善しない (Abstract LBA9002)

センチネルリンパ節生検陽性のメラノーマ患者に対する拡大リンパ節郭清術は不要である可能性がある

Extensive lymph node dissection may not be necessary for patients with melanoma with a positive sentinel node biopsy

リンパ節転移陽性患者のメラノーマ腫瘍周囲のリンパ節郭清は生存率を改善しない、と第51回American Society of Clinical Oncology年次集会で発表された。原発腫瘍を外科的に切除した後、ステージIIIメラノーマ患者483人が経過観察のみの群または完全リンパ節郭清（CLND）群にランダムに割り付けられた。微小転移巣を有する患者のみがスタディに含まれた。患者らの追跡期間中央値は35か月であった。経過観察群では、14.6%の患者がリンパ節局所転移を来したのに対し、CLND群では8.3%であった。しかし、スタディ対象者全体において、5年無再発率（p=0.72）、無遠隔転移率（p=0.76）またはメラノーマ特異的生存率（p=0.86）に関しては治療による有意差はなかった。センチネルリンパ節にがんが認められた患者は、メラノーマ再発および転移のリスクが高いと考えられている。世界的に、これらの患者にはCLNDを行うことが推奨されている。今回のスタディは、治療を変え不必要な手術やそれによる副作用から何千人もの患者を救うのに役立つ可能性が高い。

Full Text

A randomized study presented by researchers at the American Society of Clinical Oncology's 51st Annual Meeting finds that surgical removal of the lymph nodes surrounding a melanoma tumor after a positive lymph node biopsy does not improve survival. The study will likely change practice and conclude a long-standing debate about the role of this approach, called complete lymph node dissection (CLND). More importantly, the new knowledge gained from this study will help spare thousands of patients with melanoma from unnecessary surgery and its significant side effects.

Patients who have cancer detected in the sentinel lymph node upon biopsy are deemed to be at increased risk of melanoma recurrence and metastasis. Worldwide, it is recommended that such patients undergo CLND.

CLND is an extensive surgical procedure that involves removal of entire groups of lymph nodes. It carries the risk of debilitating side effects, including infection, nerve damage and lymphedema. According to the authors, lymphedema can occur in more than 20% of patients and persist long-term in 5-10% of patients.

"I think that our study is the beginning of the end of a general recommendation of complete lymph node dissection for patients with positive sentinel nodes," said senior study author Claus Garbe, MD, a professor of dermatology at the University of Tübingen in Tübingen, Germany. "However, it is possible that this surgery may provide a smaller survival advantage than this study could detect. So, doctors may want to discuss this finding with their patients to help them decide whether this procedure is right for them."

Following surgery to remove the primary tumor, 483 patients with stage III melanoma and a positive lymph node biopsy were randomly assigned to observation only or CLND. Patients in the observation group were closely monitored for signs of disease recurrence – they underwent a lymph node ultrasound exam every three months and CT/ MRI or PET scans every six months. Patients in the CLND group followed the same schedule of check-ups after CLND.

Patients had a median follow-up of 35 months. In the observation group, 14.6% of patients developed lymph node regional metastases, compared to 8.3% in the CLND group. However, the differences in three and five-year recurrence-free survival, distant metastases-free survival, and melanoma-specific survival were not statistically significant between the two groups. In this study, a survival difference of 10% or higher between the two treatment groups was considered statistically significant based on the study design.

Only patients with micrometastases were included in this study. According to the authors, CLND will continue to be recommended for patients with larger macrometastases.

Another analysis of this study is planned in three years; however, Dr. Garbe stated it is unlikely that the overall findings of the study will change, because prior research has shown that the majority (roughly 80%) of melanoma recurrences happen in the first three years of initial diagnosis.

Another ongoing CLND randomized trial, MSLT-II, is much larger and designed to detect an even smaller (5%) difference in survival. However, the final results from MSLT-II are not expected until 2022.

ASCO Expert Lynn Schuchter, MD, FASCO noted that "This is the first study to offer solid evidence that many patients with melanoma don't need extensive lymph node surgery. The findings should reduce the use of an approach that we have long assumed to be optimal. This is great news for patients, who can forego extensive surgeries without compromising their survival chances."

This study received funding from German Cancer Aid.

ASCO2015特集

口腔がんにおける頸部リンパ節手術の最良のタイミング (Abstract LBA3)

早期口腔がん患者に対する予防的頸部郭清は生存率を改善する

Preventive neck lymph node surgery improves survival for patients with early-stage oral cancer

第51回American Society of Clinical Oncology年次集会で発表されたランダム化第III相試験により、早期口腔がん患者の最良の頸部リンパ節手術時期に関する長期にわたる疑問が解決した。選択的頸部郭清術（END）として知られる予防的アプローチが、リンパ節転移を来した段階で行われる治療的頸部郭清術（TND）に比べ、生存率を改善し再発率も低下させることを示している。この試験では、早期口腔扁平上皮がん患者596人がENDまたはTNDにランダムに割り付けられた。最初の患者500人の中間解析の結果、ENDではTNDと比べ死亡リスクが37%低下したことが示された。ENDは3年全生存率を絶対的に12.5%増加させ（80%対67.5%）、これは統計学的に有意であった。ENDはまた、再発または死亡リスクを56%低下させ、3年無病生存率（69.5%対45.9%）の絶対的増加は23.6%と大きかった。これらの結果は、この疾患の標準治療としてENDを確固たるものにした。筆者らによると、頸部リンパ節郭清の唯一のマイナス面は5～40%の患者に発現する何らかの肩機能不全を来す可能性である。

Full Text

A randomized phase III study presented by researchers at the American Society of Clinical Oncology's 51st Annual Meeting resolves long-standing questions about the optimal timing of neck lymph node surgery for patients with early-stage oral cancer. It shows that a preventive approach, known as elective neck dissection (END), both improves survival and lowers recurrence rates compared to therapeutic neck dissection (TND) performed at the time of nodal occurrence.

Oral cancer affects more than 300,000 people worldwide and is especially common in parts of the world where tobacco use is high. Tobacco use and excessive alcohol consumption are estimated to account for 90% of oral cancer diagnoses.

While early oral cancer is often cured with surgery to remove the tumor, it can come back and spread to lymph nodes in the neck. Physicians have long debated whether removing surrounding lymph nodes is essential at the time of the primary oral cancer surgery (END) or if it is optimal to wait until a patient has relapsed (TND).

"Our study is the first to conclusively prove that more lives can be saved with elective neck dissection. This answers a question doctors have been asking for over 50 years, for the treatment of thousands of patients," said lead study author Anil D'Cruz, MBBS, MS, FRCS, Professor and Chief, Department of Head and Neck Surgery at Tata Memorial Centre in Mumbai, India. "Armed with the results of this study, doctors will be able to confidently counsel patients that adding neck surgery to their initial treatment is worthwhile."

In this trial, conducted at Tata Memorial Centre between 2004 and 2014, 596 patients with early stage oral squamous cancer were randomly assigned to END or TND. An interim analysis of the first 500 patients showed that END resulted in a 37% reduction in risk of death compared to TND. END was associated with a 12.5% absolute increase in three-year overall survival (80% vs. 67.5%), which was statistically significant.

END also resulted in a 56% reduction in the risk of relapse or death with a large 23.6% absolute increase in three-year disease-free survival (69.5% vs. 45.9%). In essence, there were eight fewer deaths for every 15 fewer relapses with elective neck dissection, firmly establishing it as the standard of care in this disease.

According to the authors, the only downside of neck dissection – a procedure that involves the removal of lymph nodes in the neck – is that it may be associated with some degree of shoulder dysfunction, affecting 5-40% of patients. This is because the nerve that supplies the large muscles associated with shoulder movement traverses the field of surgical dissection. Future research should focus on techniques that could minimize this complication.

As there have been no strong clinical practice recommendations advocating neck dissection with early oral cancers to date, there has been gross variability in practice the world over. This study conclusively shows that elective neck dissection should be the standard of care for patients with early oral cancer.

"This study provides long-awaited answers to a question doctors worldwide have struggled with. We never want to do more surgery than we have to, but for patients with early oral cancer, we now know that more extensive surgery prolongs lives," says ASCO Expert Jyoti D. Patel, MD.

This study received funding from the institutional research grants of the Tata Memorial Centre.

ASCO2015特集

モノクローナル抗体は非ホジキンリンパ腫の寛解を2倍にする (Abstract LBA8502)

Obinutuzumabは再発性緩徐進行性非ホジキンリンパ腫の寛解期間を2倍にする

Obinutuzumab doubles remission duration in patients with relapsed, indolent non-Hodgkin lymphoma

第III相試験の中間解析の結果、緩徐進行性非ホジキンリンパ腫（NHL）に対し標準的なベンダムスチン治療にCD20モノクローナル抗体obinutuzumabを追加することによりNHLの進行が遅延するとの研究結果が、第51回American Society of Clinical Oncology年次集会で発表された。スタディでは様々なタイプのNHL患者396人を対象とし、うち最も多いのが濾胞性リンパ腫であった。この疾患の標準的な初回治療は、化学療法と分子標的治療薬リツキシマブの併用である。多くの患者が最終的にはリツキシマブ耐性となり、その後の治療選択肢は限られている。Obinutuzumabは、B細胞リンパ腫細胞を含む全てのB細胞の表面に存在するCD20蛋白を標的とする。患者はベンダムスチン単独治療群とベンダムスチンとobinutuzumabの併用後にobinutuzumab単独療法を受ける群とにランダムに割り付けられた。もはやリツキシマブ療法が有益でなくなった患者において、新たな併用療法施行後の平均寛解期間は29.2か月であったのに対し、ベンダムスチン単独群では14か月であった。これらの有望な結果に基づき、トライアルは早期に中止された。Obinutuzumabによる全生存率への有益性の可能性を確定するために長期追跡が必要である、と筆者らは述べている。

Full Text

Interim analysis of a phase III study finds that adding the new anti-CD20 monoclonal antibody obinutuzumab to standard bendamustine chemotherapy significantly delays progression of indolent non-Hodgkin lymphoma (NHL) according to researchers at the American Society of Clinical Oncology's 51st Annual Meeting. Among patients for whom rituximab therapy no longer provided benefit, the average duration of remission was 29.2 months after receiving the new combination vs. 14 months after bendamustine alone. The trial was stopped early based on these encouraging results.

"Unfortunately, there is yet no cure for indolent lymphoma, so the overall goal of treatment is to increase the amount of time patients remain symptom-free and in remission. The fact that this new approach doubled average remission time marks a major step forward for our patients," said lead study author Laurie Helen Sehn, MD, MPH, a medical oncologist at the BC Cancer Agency in Vancouver, Canada. "Obinutuzumab may offer patients the chance to stay well for a significantly longer period of time, putting off the need for additional chemotherapy."

Indolent NHL is a very common type of lymphoma. The standard initial treatment for this disease is a combination of chemotherapy and the targeted drug rituximab. The majority of patients ultimately become resistant to rituximab, and such patients have limited options for further treatment.

Obinutuzumab targets the CD20 protein, which is located on the surface of all B cells, including B-cell lymphoma cells. Previous research suggested that when monoclonal antibodies attach to this protein, some lymphoma cells die, and others appear to become more sensitive to chemotherapy.

While obinutuzumab has been tested in smaller clinical trials in various types of lymphoma, this is the first randomized phase III trial to assess the potential benefit of obinutuzumab in patients with NHL.

The study included 396 patients with various types of NHL, the most common being follicular lymphoma. The patients were randomly assigned to treatment with bendamustine alone or a combination of bendamustine and obinutuzumab followed by obinutuzumab single-agent therapy.

After an average follow-up of 21 months, the median investigator-assessed progression-free survival was 14 months for bendamustine alone vs. 29.2 months for the combination arm. The median progression-free survival by independent review has not been reached. Dr. Sehn noted that longer follow-up is needed to determine the potential overall survival benefit associated with obinutuzumab.

In general, there were no unexpected side effects or safety concerns from the combination regimen. Low white blood cell counts and infusion-related reactions were slightly more frequent in the combination arm compared to the bendamustine arm. The rates of low platelet counts, anemia and pneumonia were higher in the bendamustine alone arm.

"It's encouraging to see such impressive results for a novel anti-CD20 monoclonal antibody in a difficult-to-treat patient population such as those with rituximab-refractory indolent non-Hodgkin lymphoma," says ASCO Expert Merry-Jennifer Markham, MD. "The fact that this approach stalled cancer progression by more than a year will be good news to patients, who urgently need additional treatment options."

This study received funding from Genentech Inc. and F. Hoffmann-La Roche Ltd.

ASCO2015特集

骨髄線維症の新規治療薬は血小板減少症を伴っていても有効である (Abstract LBA7006)

PERSIST：新規JAK阻害剤は血小板数が減少している患者であっても症状軽減に有効であることが証明された

PERSIST: Novel JAK inhibitor proves effective for easing symptoms of myelofibrosis even for patients with low platelet counts

骨髄線維症患者を対象としたPERSISTスタディの結果、pacritinibは血小板が非常に減少した患者であっても現状で利用可能な最良の治療（BAT）よりも有効であることが示唆された。このスタディにおいて、327人の患者がpacritinibまたはBATによる治療群にランダムに割り付けられた。BAT治療群患者はエリスロポエチン刺激薬、免疫調節薬（例えば、サリドマイド、レナリドミド）、およびヒドロキシウレアなどの承認適応外の骨髄線維症治療薬を定期的に投与された。このスタディは血小板数が非常に少ない患者を組み入れたため、ルキソリチニブは安全ではないと思われ、あえて除外した。Pacritinibの効果は治療開始後4週と、早い時点で認められた。24週後には、pacritinib群患者の19.1%において脾臓サイズが減少したのに対し、BAT群におけるその割合はわずか4.7%であった（p=0.003）。血小板数が最も少ない患者サブグループにおいて、脾臓縮小はpacritinib 群の33.3%に認められたのに対し、BAT群では0%であった。Pacritinib群患者は悪液質、盗汗、発熱、および骨痛などの症状の軽減が大であった。このスタディ結果は、第51回American Society of Clinical Oncology年次集会で発表された。

Full Text

Findings from the PERSIST study of patients with myelofibrosis suggest that pacritinib is significantly more effective than best available therapy (BAT), which includes a range of off-label treatments, even in patients with very low platelet counts. At 24 weeks of treatment, 19.1% of patients on the pacritinib arm experienced spleen shrinkage, compared to only 4.7% of patients on the BAT arm. The study findings were presented at the American Society of Clinical Oncology's 51st Annual Meeting.

Myelofibrosis is a rare blood cancer, and spleen enlargement is a common, debilitating symptom. Pacritinib also improved a range of additional symptoms and eliminated the need for blood transfusion in a quarter of patients who had previously been dependent on transfusions due to low blood counts.

This experimental therapy was also beneficial for a subgroup of patients with thrombocytopenia, for whom no FDA approved therapy exists.

"There is a huge unmet clinical need for patients with myelofibrosis. Only one drug is currently FDA approved for the disease, and it is not safe for patients with low platelet counts," said lead study author Ruben A. Mesa, MD, Deputy Director of the Mayo Clinic Cancer Center in Scottsdale, AZ. "We were encouraged to see that pacritinib was safe and effective in the trial, even in patients with severely low blood counts."

There is currently no cure for myelofibrosis, besides allogeneic hematopoietic stem cell transplant, which is an option that is not feasible for many, and the only FDA approved treatment is a JAK inhibitor, ruxolitinib. Several other agents targeting JAK proteins are in development.

In PERSIST, 327 patients were randomly assigned to treatment with pacritinib or BAT. Patients on the BAT arm received therapies that are routinely prescribed off-label for myelofibrosis, such as erythropoietin stimulating agents, immunomodulatory drugs (e.g., thalidomide, lenalidomide), and hydroxyurea. Ruxolitinib was intentionally excluded because this study included patients with very low platelet counts, for which this drug is not deemed to be safe.

The effects of pacritinib were seen as early as four weeks of starting treatment. At 24 weeks, 19.1% of patients in the pacritinib arm had a reduction in spleen size, compared to only 4.7% in the BAT arm (p=0.003). In the subgroup of patients with the lowest platelet counts (those who are not candidates for ruxolitinib), spleen shrinkage occurred in 33.3% of patients in the pacritinib arm and 0% in the BAT arm.

Compared to patients on the BAT arm, patients on the pacritinib arm experienced a greater degree of relief from symptoms such as cachexia, night sweats, fever, and bone pain. The vast majority (79%) of patients on the BAT arm eventually crossed over to the pacritinib arm.

Pacritinib also helped alleviate anemia in some patients; among patients who had been dependent on red blood cell transfusion, 25.7% no longer needed the procedure. In contrast, none of the patients on the BAT arm became transfusion independent.

The most common side effects of pacritinib were diarrhea, nausea, and vomiting. The symptoms typically lasted less than one week and few patients discontinued treatment due to side effects.

Longer follow up is needed to determine if pacritinib improves survival. The ongoing PERSIST-2 phase III trial is exploring pacritinib for the treatment of patients who have low blood platelet counts due to their disease, or due to their therapy. Dr. Mesa remarked that pacritinib may be an attractive agent to combine with other therapies, as it does not cause low platelet counts.

ASCO President-Elect Julie M. Vose, MD, MBA, FASCO commented on the study. "This is exciting news for patients with myelofibrosis, a blood cancer for which the discovery of new treatments has been slow. It's especially encouraging that pacritinib is effective in some patients with low blood counts, since they are not ideal candidates for the only other FDA approved therapy."

This study received funding from CTI BioPharma Corp.

ASCO2015特集

治療により進行乳がんの進行が抑制される (Abstract LBA502)

PALOMA-3：新たな分子標的治療薬palbociclibはホルモン受容体陽性乳がんの進行を遅延させる

PALOMA-3: Novel targeted drug palbociclib slows progression of hormone receptor-positive breast cancer

前治療歴のあるエストロゲン受容体陽性ヒト上皮成長因子受容体2陰性（HR+/HER2-）進行乳がん患者において標準ホルモン療法（フルベストラント）にpalbociclibを併用することで疾患コントロール期間が2倍以上に延長したとのPALOMA-3スタディの結果が第51回American Society of Clinical Oncology年次集会で発表された。Palbociclibは、サイクリン依存性キナーゼ（CDKs）4および6の新規経口阻害薬で、画期的新薬である。先行研究から、CDK4およびCDK6はエストロゲン陽性乳房腫瘍の増殖を促進する重要な蛋白の一部であることが示されている。HR+/HER2-乳がんの女性がpalbociclibとフルベストラント併用またはプラセボとフルベストラント併用群にランダムに割り付けられた。全ての患者が初回ホルモン療法後に悪化または再発した転移がんを有しており、21%は閉経前であった。筆者らによると、PALOMA-3は分子標的治療薬の最初の登録研究の１つであり―若年、閉経前女性を含む進行乳がんにおけるホルモン療法併用スタディの1つである。この中間解析の時点で、疾患進行までの平均期間はpalbociclib群で9.2か月であったのに対しプラセボ群では3.8か月であった。閉経前女性と閉経後女性とで有益性は同等であった。今回の中間解析において有益性が認められたことから、トライアルは早期に中止となった。

Full Text

The phase III registration study PALOMA-3 reports that adding the investigational targeted agent palbociclib to standard hormonal therapy (fulvestrant) more than doubled the duration of disease control, delaying disease progression by roughly five months in women with previously treated, hormone receptor-positive, human epidermal growth factor receptor 2 negative (HR+/HER2-) advanced breast cancer. The study results were reported at the American Society of Clinical Oncology's 51st Annual Meeting.

This trial was stopped early based on efficacy seen in the interim analysis.
Approximately 75% of all breast cancers are hormone receptor-positive (HR+), HER2 negative,2 and palbociclib in combination with hormonal therapy could become a very effective treatment option after initial hormonal therapy for women with HR+, HER2- advanced breast cancer.

"After initial hormonal therapy stops working in metastatic breast cancer, the next step is typically chemotherapy, which can be effective, but the side effects are often very difficult for women," said lead study author Nicholas C. Turner, a consultant medical oncologist at The Royal Marsden and a team leader at The Institute of Cancer Research, London, United Kingdom. "This relatively easy-to-take new drug can substantially delay the point when women need to start chemotherapy, making this an exciting new approach for women."

Palbociclib is a novel, first-in-class oral drug that blocks cyclin dependent kinases (CDKs) 4 and 6. Prior research has shown that CDK4 and CDK6 are among the key proteins that fuel the growth of hormone receptor-positive breast tumors. Strong preclinical evidence supports combining CDK4 and CDK6 inhibitors with hormonal therapy. Fulvestrant is one of the most active hormone therapies for patients with HR+/ HER2- advanced breast cancer.

Women with HR+/HER2- breast cancer were randomly assigned to palbociclib with fulvestrant or placebo with fulvestrant. All patients had metastatic disease that had worsened or relapsed after initial hormonal therapy, and 21% were premenopausal. According to the authors, PALOMA-3 is one of the first registration targeted therapy–hormone therapy combination studies in advanced breast cancer to include younger, premenopausal women.

At the time of this interim analysis, the average time to disease progression was 9.2 months in the palbociclib arm compared to 3.8 months in the placebo arm. Comparable benefits were seen in pre- and postmenopausal women.

Longer follow-up is needed to determine the effect of palbociclib on overall survival. Quality of life data were collected and will be reported at a later date.
The palbociclib combination was generally well tolerated, with only 2.6% of patients having to stop treatment due to side effects, the most common being blood count abnormalities. Despite frequent occurrences of low white blood cell counts, the rates of a serious complication known as febrile neutropenia were very low (0.6%), the same in both treatment groups.

Another study known as PALOMA-2 is exploring the efficacy of palbociclib as a therapy for advanced breast cancer not previously treated with hormonal therapy. Dr. Turner noted that researchers are also looking at the possibility of using this therapy in women with early-stage hormone receptor-positive breast cancer.

Earlier this year, the FDA granted palbociclib accelerated approval for use in combination with letrozole for women with metastatic estrogen receptor positive (ER+), HER2- breast cancer who have not yet received hormonal therapy for their metastatic disease. The approval was granted based on results of a prior phase II study, PALOMA-1.

"For women with advanced breast cancer, it's remarkable to be able to stall disease progression and stave off the need for chemotherapy for months with a simple pill," commented ASCO Expert Don S. Dizon, M.D.. "In one of the most common forms of advanced breast cancer, palbociclib works in both older and younger women."

This study received funding from Pfizer.

ASCO2015特集

進行肝臓がんに対する免疫療法 (Abstract LBA101)

早期段階トライアルにおいてnivolumabは進行肝臓がんにおいて非常に有望な作用を示した

Nivolumab shows highly promising activity in advanced liver cancer in early stage trial

第51回American Society of Clinical Oncology年次集会で報告された第I/II相スタディの結果、進行肝臓がんにおいてnivolumabは安全で有効であることが示唆された。スタディ登録患者の75%が過去に全身療法を受け、うち68%が現在の標準治療であるソラフェニブを投与された。Nivolumabは経静脈的に2週ごとに最長2年間投与された。今回のスタディの第I相の結果に基づくと、評価可能な患者42人中8人(19%)において抗PD-1抗体が奏効し、腫瘍縮小が30%を超えた。2人の患者は完全寛解した。持続的な奏効が認められ50%においては12か月以上持続し、ほとんどの患者が治療を継続した。さらに、48%の患者において腫瘍増殖が停止し、その期間は最長で17か月を超えた。12か月後の全生存率は62%であった。NivolumabはB型肝炎またはC型肝炎のウイルス感染が持続していても安全であり、忍容性は良好であった。これらの結果は大規模スタディで検証する必要はあるが、この試験は免疫チェックポイント阻害による免疫療法が肝臓がん治療において役割を果たすであろうことを示す初めてのものである、と筆者らは指摘している。

Full Text

Findings from a phase I/II study reported at the American Society of Clinical Oncology's 51st Annual Meeting suggest that nivolumab is safe and effective in advanced liver cancer. Based on the results of the phase I part of the study, eight (19%) of the 42 evaluable patients responded to the anti-PD-1 antibody with tumor reduction beyond 30%. More importantly, the responses have been durable and surpassed 12 months in four patients. The overall survival rate at 12 months was 62%.

Patients with advanced liver cancer are in particular need of new treatments. There is currently only one FDA-approved systemic treatment for advanced liver cancer, the multi-targeted tyrosine kinase inhibitor, sorafenib. However, just 2% of patients have an objective tumor response (more than 30% shrinkage) to sorafenib, and the average overall survival is 10-11 months.

"We are encouraged to see that nivolumab was safe overall, and the response rate as well as preliminary survival data look quite promising," said lead study author Anthony B. El-Khoueiry, M.D., an associate professor of clinical medicine and phase I program director at the University of Southern California Norris Comprehensive Cancer Center in Los Angeles, CA. "While we have to verify this early signal in larger studies, this is one of the first signs that immunotherapy with immune checkpoint inhibitors will have a role in the treatment of liver cancer."

Liver cancer is the leading cause of cancer death worldwide, accounting for more than 600,000 deaths each year.

Seventy-five percent of the patients enrolled on the study had previously received systemic therapy, including 68% who had received sorafenib. Nivolumab was given intravenously every two weeks for up to two years.

The overall response rate was 19%, with eight patients experiencing objective tumor shrinkage beyond 30%, and two having complete remissions. The responses were durable, with 50% lasting beyond 12 months as most patients continued on treatment. In addition, tumors stabilized in 48% of patients, with the longest case lasting beyond 17 months.

Nivolumab was safe and well tolerated, even in patients with ongoing hepatitis B or C infections. Specifically, there have not been any safety concerns related to flares of hepatitis B infection or worsening viral infection. The majority of the side effects were mild to moderate in nature with abnormal liver enzymes, rash, and elevation of amylase and lipase being the most common; the abnormal liver enzymes and elevated amylase and lipase were not accompanied by any significant clinical symptoms.

Dr. El-Khoueiry remarked that the findings from this early trial open the door to a new class of drugs for patients with liver cancer. "While these results are preliminary and limited to a small number of patients, they remain exciting and provide strong justification for more studies of nivolumab and other immunotherapy approaches for patients with advanced liver cancer," he said.

"PD-1 immunotherapies continue to break new ground in diseases where nothing else seems to work well. The fact that this drug might stop advanced liver cancer in its tracks for months, even a year, is great news for patients," said ASCO Expert Lynn Schuchter, M.D., FASCO. "To understand the full impact of this approach, however, larger trials are needed."

This study received funding from Bristol-Myers Squibb.

ASCO2015特集

進行の速い軟部組織肉腫に対する生存の有益性が認められた (Abstract LBA10502)

エリブリンは進行脂肪肉腫および平滑筋肉腫の患者の全生存期間を延長する

Eribulin extends overall survival for patients with advanced liposarcoma and leimyocarcoma

第51回American Society of Clinical Oncology年次集会で報告されたランダム化第III相トライアルの結果、2ライン以上の前治療歴の後に増悪した中等度または高度進行脂肪肉腫または平滑筋肉腫患者に対する新たな治療の有効性が示された。スタディにおいて、進行平滑筋肉腫または脂肪肉腫とも呼ばれる脂肪細胞性肉腫の患者452人が、エリブリンまたはダカルバジン治療を疾患が増悪するまで行う群にランダムに割り付けられた。全ての患者のがんは過去に2回以上の治療を受けたが増悪した。全生存期間中央値はエリブリン群で13.5か月であり、ダカルバジン群で11.5か月であった（p=0.0169）。エリブリンの最も多い副作用は白血球減少、倦怠感、嘔気、脱毛、および便秘であり、8%の患者が副作用のために治療を中止した。筆者によると、この進行の速い疾患群の全生存期間改善を示した、これは初めての第III相試験である。彼らは、まれで悪性度の高いこの疾患群におけるアンメット・メディカルニーズを考えると、今回の結果は臨床的に重要なものである、と結論付けている。

Full Text

Findings from a randomized phase III trial reported at the American Society of Clinical Oncology's 51st Annual Meeting point to a promising new therapy for patients with advanced intermediate or high grade liposarcoma or leiomyosarcoma whose disease worsened after two or more lines of initial therapies. Patients treated with the chemotherapy drug eribulin had a two-month increase in median overall survival compared to those treated with the standard drug dacarbazine.

According to the authors, this is the first randomized phase III study to show an improvement in overall survival in patients with this aggressive family of diseases.
"Soft-tissue sarcomas are relatively rare and can be very difficult to treat. The efficacy of available drugs for initial therapy is very unsatisfactory, and patients whose disease progresses despite two or more lines of treatment have a very poor prognosis," said lead study author Patrick Schöffski, M.D., MPH, Head of Department of General Medical Oncology, University Hospitals Leuven in Leuven, Belgium. "For a disease where such few treatment options exist, a two-month improvement in survival is significant. The more treatments our patients have access to, the better their chances of improving life expectancy."

Soft-tissue sarcoma is a diverse family of rare diseases, and liposarcomas and leiomyosarcomas are among the more common types. Patients with advanced, metastatic soft-tissue sarcoma have poor outcomes, typically with survival of one year or less. There are currently few treatment options available, particularly at the point the disease worsens or further spreads to other parts of the body despite prior therapy.

In the study, 452 patients with advanced leiomyosarcoma or adipocytic sarcoma, which is also called liposarcoma, were randomly assigned to treatment with eribulin or dacarbazine until disease progression. All patients had cancers that had worsened upon receiving two or more prior treatments.

The median overall survival was 13.5 months in the eribulin group and 11.5 months in the dacarbazine group (p=0.0169). The authors conclude that this is a clinically meaningful result given the unmet need in this rare, hard-to-treat family of diseases.

The most common side effects associated with eribulin were low white blood cell counts, fatigue, nausea, hair loss, and constipation, and 8% of patients stopped treatment due to side effects. Low platelet counts were more common in the dacarbazine group compared to the eribulin group. Grade 3 and 4 treatment-related side effects occurred more frequently with eribulin than dacarbazine.

Eribulin belongs to a class of anticancer drugs known as microtubule inhibitors, which block cell division. It was originally derived from a natural source — a sea sponge.

Several additional analyses are ongoing, including quality of life analysis, subgroup analysis and biomarker tests. The results of those analyses will be reported at a later date.

ASCO Expert Gary K. Schwartz, M.D. commented on the study: "In a disease that has been notoriously difficult to treat, even small steps forward are worthwhile. These findings also remind us that our work is far from finished. The survival gain seen with eribulin must be weighed against the burden of side effects patients experienced."

This study received funding from Eisai Inc.

ASCO2015特集

脳転移治療中の認知機能改善(Abstract LBA4)

全脳照射を受ける患者は放射線外科治療を受ける患者よりも認知機能低下がより多い

Cognitive decline more common in patients receiving whole brain radiation therapy than radiosurgery

第III相試験により、認知機能に対するアジュバント全脳照射（WBRT）の影響についての長年の論議に追加情報が提供された。1～3個の小さい脳転移に対し放射線外科治療後にWBRTを受けた患者は、放射線外科治療を受けた患者に比べ認知機能低下を来す確率が高いとの研究結果が、第51回American Society of Clinical Oncology年次集会で発表された。さらに、WBRTは脳転移の増殖抑制には役立ったが、患者の生存期間は有意に延長しなかった。このスタディにおいて、213人の患者が放射線外科治療または放射線外科治療後にWBRTを受ける群にランダムに割り付けられた。全ての患者が1～3個の小さな脳転移（最大径3㎝）を有していた。3か月後に認知機能低下を来していたのはWBRT群（92%）において放射線外科治療群（64%）よりも多かった。特に、WBRTを受けた患者は即時想起（30%対8%）、遅延想起（51%対20%）、および言葉によるコミュニケーション（19%対2%）における低下が著しかった。このスタディのQOLに関するデータ解析はまだ終了していない。

Full Text

A federally funded phase III trial provides additional information regarding a long-standing discussion about the impact of adjuvant whole brain radiation therapy (WBRT) on cognitive function. Patients with 1-3 small brain metastases who received radiosurgery followed by WBRT were more likely to experience cognitive decline than those who received radiosurgery alone according to research presented at the American Society of Clinical Oncology's 51st Annual Meeting. Furthermつore, WBRT did not significantly extend patient survival, though it did help control growth of brain metastases.

Patients with limited brain metastases often receive radiosurgery. Brain metastases are removed by conventional surgery in only a select minority of patients.

"We used to offer whole brain radiation early on, but we now know that the toxicities of this therapy are worse for the patient than cancer growth or recurrences in the brain," said senior study author Jan C. Buckner, M.D., a professor of oncology at Mayo Clinic in Rochester, MN. "We expect that practice will shift to reserve the use of whole brain radiation therapy for salvage treatment and end-stage palliative care."

In the study, 213 patients were randomly assigned to receive radiosurgery or radiosurgery followed by WBRT. All patients had 1-3 brain small brain metastases (up to 3 cm in width). At three months, more patients experienced cognitive decline in the WBRT group (92%) than in the radiosurgery group (64%).

Specifically, patients who received WBRT had a greater decline in immediate recall (30% vs. 8%), delayed recall (51% vs. 20%), and verbal communication (19% vs. 2%). The analysis of quality of life data from this study has not yet been completed. The difference in overall survival was not statistically significant between the two treatment groups.

According to the authors, the findings of this study have broad implications for oncology practice, as brain metastases are a common complication in cancer care. Melanoma and cancers of the lung, breast and colon spread to the brain especially often. Patients with bladder, kidney and gynecologic cancers can also develop brain metastases.

Dr. Buckner remarked that while adjuvant WBRT continues to be an option for patients with resected brain metastases, the ongoing NCCTG/Alliance trial comparing WBRT to stereotactic radiosurgery to the surgical cavity in patients with resected brain metastasis will eventually determine which treatment approach is better.

ASCO Expert Brian Michael Alexander, M.D. commented on the study: "This study will help shape treatment decisions for thousands of current and future patients. As doctors, we want the very best for our patients, and sometimes giving less treatment offers the better result. In patients treated with radiosurgery, the benefits of adding whole brain radiation must be weighed against the risks and side effects of treatment, and this study helps us identify the tradeoffs involved."

This study received funding from the National Institutes of Health.

ASCO2015特集

小児腎がんの予後改善 (Abstract 10009)

標準治療の強化により高リスクのWilms腫瘍の治癒率が上昇する

Augmenting standard therapies increase cure rates for high-risk Wilms tumor

2つの第III相試験の結果、薬剤を追加することによる治療強化は高リスクWilms腫瘍の小児の予後を改善する、と第51回American Society of Clinical Oncology年次集会で発表された。このスタディは、いわゆる予後良好な組織型のWilms腫瘍（小児腎腫瘍の75%を占める）の小児に焦点を当てた。これらの腫瘍のうち、約5～6%が染色体1pと16qにヘテロ接合性の消失（LOH）として知られる染色体異常を腫瘍内に有していた。研究者らは過去に、LOH 1pおよび16qを有する患者は再発リスクが高いことを明らかにした。LOH 1pおよび16qはステージI/IIの患者35人、およびステージIII/IVの患者52人において検出された。ステージI/IIの患者に対しては標準治療（ビンクリスチン／アクチノマイシンDによる化学療法）にドキソルビシンを追加し強化された。ステージIII/IVの患者はRegimen M（ビンクリスチン／アクチノマイシンDによる化学療法および放射線療法）に4サイクルのシクロフォスファミド／エトポシドの外来での投与を追加することにより強化された。先行研究では、これらの患者の4年無再発生存率はステージI/IIで74.9%であり、ステージIII/IVでは65.9%であった。今回の新たなスタディにおいて、強化療法はこの率をステージI/IIで83.9%、ステージIII/IVで91.5%に上昇させた。

Full Text

Two phase III Children's Oncology Group studies found that augmenting therapy with additional drugs improves outcomes for children with a high-risk form of Wilms tumor according to researchers at the American Society of Clinical Oncology's 51st Annual Meeting. These patients have a specific chromosomal abnormality associated with poorer prognosis. In prior research, such patients had four-year relapse-free survival rates of 74.9% for stage I/II disease and 65.9% for stage III/IV disease. In the new studies, augmented therapy increased the rates to 83.9% for stage I/II and 91.5% for stage III/IV disease.

"Tailoring therapy to match each patient's risk for relapse has been a major focus of pediatric oncology. For cancers with a low risk of recurrence, we strive to decrease therapy and minimize exposure to potentially toxic agents. On the other hand, we want to augment the therapy for those patients who are at higher risk of relapse so that we can hopefully increase the chance for cure," said lead study author David B. Dix, M.D., a physician at the British Columbia Children's Hospital in Vancouver, Canada. "Our study is an example of successful augmentation of therapy for a higher risk group. We were very encouraged to see that augmentation of therapy can overcome the negative influence of a biologic marker in children with Wilms tumor."

Wilms tumor is a rare form of kidney cancer that mainly affects children under the age of five years. This study focused on children with so-called favorable histology Wilms tumor, which accounts for 75% of childhood renal cancers. Of those, about 5-6% of have a chromosome abnormality in the tumor that is known as loss of heterozygosity (LOH) on chromosomes 1p and 16q. Researchers previously found that patients with LOH 1p and 16q have a higher risk of relapse.

In the studies, LOH 1p and 16q was detected in 35 patients with stage I/II disease and 52 with stage III/IV disease. For patients with stage I/II disease, the standard therapy (vincristine/dactinomycin chemotherapy) was augmented with the addition of doxorubicin. Patients with stage III/IV disease received Regimen M: the standard therapy (vincristine/dactinomycin/doxorubicin and radiation therapy) was augmented with 4 cycles of outpatient cyclophosphamide/etoposide.

At a median follow-up of 3.6 years, the four-year relapse-free survival rates were 83.9% for stage I/II disease and 91.5% for stage III/IV disease. When comparing these rates to outcomes with standard treatment regimens (75% for early- stage disease and 66% for late-stage disease), these studies suggest that augmentation of therapy markedly improves outcomes for patients with advanced disease. Given the small numbers in the study sample, the benefit is less clear for patients with lower stage disease but suggestive of an improved outcome.

Overall, the treatment was well tolerated. For stage I/II patients, augmented therapy was not associated with any significant short term increase in side effects. For stage III/IV patients, the most common severe side effect of Regimen M was suppression of bone marrow function, occurring in 60% of patients; however, the side effect was manageable. According to the authors, Regimen M substantially reduces the number of patients who would otherwise have to undergo very intensive relapse therapy. However, the regimen is predicted to be associated with some risk of reduced fertility. The authors recommend a clear discussion with families regarding the risks and benefits of augmented therapy for these higher risk patients with LOH.

ASCO President-Elect Julie M. Vose, M.D., MBA, FASCO commented on the study: "It's very encouraging that we're making progress even for kids with a rare, high-risk form of this disease. The ability to easily identify a small subset of patients with a poorer prognosis means these children can receive treatment that's right for them, while decreasing side effects for lower risk patients. And that means a better shot at surviving their cancer."

This study received funding from the National Institutes of Health.

ASCO2015特集

治療により進行前立腺がんの生存期間が延長する (Abstract 5001)

STAMPEDE：初回治療に化学療法を追加することにより進行ホルモン療法未治療前立腺がん患者の寿命が延長する

STAMPEDE: Adding chemotherapy to initial therapy extends lives of men with advanced, hormone-naïve prostate cancer

Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy（STAMPEDE）トライアルの結果、標準的なホルモン療法にドセタキセルによる化学療法を追加することにより、ホルモン治療歴のない新たに診断された進行前立腺がん患者の生存期間が改善する、と第51回American Society of Clinical Oncology年次集会で発表された。研究者らは、ホルモン療法未治療の患者2,962人をSTAMPEDEの9つの治療群のうち4つ：標準治療（SOC）、SOCとドセタキセルを6サイクル、SOCとゾレドロン酸を2年間、およびSOCとドセタキセルおよびゾレドロン酸の両者に割り付けた。約60%の患者がトライアル参加時に転移を有しており、その他は高リスク、局所進行非転移前立腺がん（リンパ節転移陰性、ステージT3/4、PSA≥40ng/mlまたはGleasonスコア8-10）を有していた。追跡期間中央値42か月後に、948人が死亡した。全生存期間はドセタキセル群においてSOC群よりも平均10か月長く（67対77か月）、相対的改善率は24%であった。転移性疾患患者においては、全生存期間における平均改善率はさらに大であった（43対65か月）。ドセタキセルはまた、全ての患者において再発までの期間を38%延長させた。

Full Text

The UK-led trial Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) found that adding docetaxel chemotherapy to standard hormone therapy markedly improves survival for men with newly diagnosed advanced prostate cancer not previously treated with hormone therapy according to researchers at the American Society of Clinical Oncology's 51st Annual Meeting. Men who received docetaxel plus standard therapy lived on average ten months longer than those who received only standard therapy. In contrast, adding zoledronic acid to standard therapy did not affect survival, and adding the combination of zoledronic acid and docetaxel was not more effective than adding just docetaxel.

"We hope our findings will encourage doctors to offer docetaxel to men newly diagnosed with metastatic prostate cancer, if they are healthy enough for chemotherapy. Men with locally advanced, non-metastatic prostate cancer may also consider docetaxel as part of upfront therapy, as it clearly delays relapse," said lead study author Nicholas David James, M.D., Ph.D., Director of the Cancer Research Unit at the University of Warwick in Coventry, United Kingdom and Consultant in Clinical Oncology at Queen Elizabeth Hospital Birmingham. "It's also clear that zoledronic acid does not benefit these patients and should not be offered as an upfront treatment for advanced prostate cancer."

STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy), is the largest randomized clinical trial of treatment for men with prostate cancer ever conducted, with more than 6,500 patients enrolled since 2005. The ongoing study has an innovative multi-stage, multi-arm design that can be modified to both assess new therapies and adapt to changes in the standard of care. The standard of care (SOC) in the continuously recruiting control arm changes as treatment patterns change. For example, radiation therapy has been added to the mainstay androgen deprivation therapy for certain patients. As the trial goes on, treatment arms that are found to be ineffective are stopped, and new arms are added to assess the efficacy of emerging treatments, such as novel hormone drugs.

At ASCO's Annual Meeting, researchers reported results on 2,962 hormone-naïve men who were assigned to four of STAMPEDE's nine different treatment arms: SOC, SOC with docetaxel for six cycles, SOC with zoledronic acid for two years, and SOC with both docetaxel and zoledronic acid. The SOC was at least three years of androgen deprivation therapy, with local radiation for suitable patients. About 60% of the patients had metastatic disease when joining the trial and the rest had high-risk, locally advanced non-metastatic prostate cancer (node-negative, stage T3/4, PSA≥40ng/ml or Gleason sum score 8-10).

After a median follow-up of 42 months, 948 men had died. Overall survival was on average ten months longer in the docetaxel arm compared to the SOC arm (67 vs. 77 months) with a relative improvement of 24%. For the subset of patients with metastatic disease, the average improvement in overall survival was even higher, 22 months (from 43 vs. 65 months). Importantly, docetaxel also extended the time to relapse by 38% in all patients.

Two previous, smaller trials have reported results on using docetaxel in the hormone-naïve metastatic setting. These trials showed conflicting results. CHAARTED in the USA reported in the plenary session of ASCO 2014 showed a survival advantage; GETUG-15 in France did not. STAMPEDE goes a long way in clarifying the role of docetaxel in men with newly diagnosed, high-risk prostate cancer. The trial also included a larger and broader patient population than those trials, comprising men with metastatic prostate cancer and 600 men with locally advanced, non-metastatic disease.

According to the authors, the overall findings of this study suggest that men with newly diagnosed metastatic prostate cancer should be offered docetaxel as part of their initial therapy. They suggest that doctors may also discuss the option of adding docetaxel with patients who have advanced, non-metastatic prostate cancer, given the reduction in risk of relapse seen in this study. However, longer follow-up is needed to determine if there is any survival advantage in men with non-metastatic disease.

While docetaxel was associated with some additional toxicity compared to SOC alone, the side effects were manageable, and very few patients discontinued docetaxel due to side effects. Results of a quality of life analysis will be reported at a later time.

The difference in survival was not statistically significant between the SOC and SOC plus zoledronic acid arm. Addition of zoledronic acid to the combination of SOC and docetaxel yielded similar outcomes as SOC with only docetaxel.

"This is the biggest trial of its kind and strongly suggests that adding chemotherapy to standard hormone therapy can extend the lives of men with advanced prostate cancer" comments ASCO President Peter Paul Yu, M.D., FACP, FASCO. "Its innovative design is exciting, and one that we may begin to see in other areas of oncology."

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