進行性小児がん治療に関する有望な結果（Abstract＃9500）

早期スタディにおいてcrizotinibはALK遺伝子異常により引き起こされる3つの小児がんに対し強力で長期持続する奏効を示した

In early study, crizotinib induces strong, long-lasting responses in three pediatric cancers driven by ALK gene abnormality

第48回American Society of Clinical Oncology学会で発表された第1相試験の結果、分子標的薬crizotinibは腫瘍の成長を停止させ、一部の症例では、進行性神経芽腫、未分化大細胞型リンパ腫（ALCL）または炎症性筋線維芽細胞性腫瘍（IMT）を有する選択された小児において全ての徴候を根絶することが示された。Crizotinibはこれらの小児がん患者において一般的に認められるALK遺伝子異常を標的とする。患者は6つの用量のcrizotinibのうちいずれかの用量を投与され、忍容性が良好な限りは同用量を継続した。その結果、ALCL患者の88%（7/8）において病変が検出されず完全寛解が認められた。奏効の持続は長期間認められ、治療を継続した患者は18か月間疾患の増悪を認めなかった。7人のIMT患者がこのトライアルに登録された。その多くが腫瘍の縮小から完全な腫瘍退縮に至るまでの実質的な有益性を最長2年間得た。神経芽腫患者27人中2人は完全寛解し、8人においては疾患が安定した。ALK異常が証明されている患者8人中2人が完全寛解した。治療が奏効したこれらの患者は疾患が増悪することなく9か月から2年以上にわたり治療を継続した。

Full Text

A Phase I study presented at the American Society of Clinical Oncology's 48th Annual Meeting has shown that the targeted drug crizotinib stalled tumor growth and, in some cases, eradicated all signs of cancer in select children with aggressive forms of neuroblastoma, anaplastic large cell lymphoma (ALCL) or inflammatory myofibroblastic tumors (IMT).

Crizotinib targets genetic abnormalities in the ALK gene, which are common in these pediatric cancers. If these promising early-phase findings are borne out in larger trials, crizotinib could become only the second effective molecularly targeted therapy for pediatric cancers. ALK abnormalities are present in 80 to 95 percent of ALCL cases, half of IMTs and 10 to 15 percent of aggressive neuroblastomas. Crizotinib was recently approved in the United States to treat adult ALK-driven lung cancers, about 5 percent of cases.

"It's remarkable that this targeted oral medication provided such a substantial benefit in these children with highly aggressive cancers, most of whom had already undergone every available therapy," said Yael Mosse, MD, assistant professor of pediatrics at the Children's Hospital of Philadelphia and the University of Pennsylvania. "Now that we know more about the drivers of some pediatric cancers, we can target those changes and treat patients in a much smarter, and potentially safer, way."

The study included 70 children whose cancer had progressed despite all standard therapies. When possible, patients' cancers were tested for ALK abnormalities, though this was not required for enrollment. Patients received one of six different doses of crizotinib – administered orally, twice a day – and remained on the drug as long as it was well-tolerated, which was the case in the vast majority of patients. By disease, researchers found:

- ALCL: 88 percent (7/8) of patients experienced a complete response, having no detectable disease. Responses have been long lasting, with patients remaining on treatment with no progression for as long as 18 months.
- IMTs: Seven patients with this rare disease were enrolled onto this trial. The majority have experienced substantial benefit, ranging from tumor shrinkage to complete tumor regression. Such responses have lasted for up to two years, with all patients still receiving therapy; these findings are important because no other available anticancer therapies are effective in this disease.
- Neuroblastoma: Overall, two of 27 patients had a complete response, and eight have had no disease progression (stable disease). Of patients with a proven ALK abnormality, two of eight patients experienced a complete response. These responders have remained on therapy for between 9 months to more than two years without progression – a notable finding given that most heavily pre-treated neuroblastoma patients on a Phase I trial experience cancer progression in 1 to 2 months.

Researchers also observed that neuroblastoma patients treated with higher doses of crizotinib – which in some cases were twice the approved adult dose – experienced demonstrable responses. This may explain why some neuroblastoma patients with proven ALK abnormalities did not respond to crizotinib, since they had received lower doses of the drug than the responders.

Dr. Mosse is the recipient of this year's James B. Nachman ASCO Junior Faculty Award in Pediatric Oncology.

ASCO2012特集

メラノーマに対する有望な新併用療法（Abstract＃8510）

進行メラノーマ患者に対する2つの分子標的治療薬併用は毒性が少なく有望な作用を示した

Combining two targeted drugs shows encouraging activity with fewer toxicities for patients with advanced melanoma

第48回American Society of Clinical Oncology学会で発表されたexpanded IBトライアルの結果、治験段階にある2つの分子標的治療薬—BRAF阻害薬dabrafenibおよびMEK阻害薬trametinib—は、がんの進行を停止し、現在の標準単剤BRAF標的治療薬のスタディで公表されたよりも皮膚副作用レベルが低いことが示された。この解析ではV600 BRAF変異を有しBRAF標的治療を受けたことのない進行メラノーマ患者を対象とした。トライアル全体では、様々な用量のdabrafenib および trametinibを投与された患者125人が含まれ、今回の解析では過去にBRAF標的治療を受けたことのない（化学療法などの前治療は許可された）、したがってBRAF標的治療抵抗歴のないサブグループの77人に焦点が当てられた。この77人の患者の無増悪生存期間中央値は7.4か月であり、過去のvemurafenib単剤スタディでみられた結果と同等であった。生存期間に関するデータは今年後半に得られる予定である。トライアル全体の125人中扁平上皮がんが発症したのはわずか2%であり、他の2%において日光角化症が発症した。一般的なしかし制御可能なその他の副作用は発熱、倦怠感および脱水などであった。

Full Text

Results from an expanded Phase IB trial presented at the American Society of Clinical Oncology's 48th Annual Meeting, show that combination therapy with two investigational targeted drugs – the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib – stalls cancer progression and with a lower level of skin side effects than published studies of the current standard single-agent BRAF-targeted therapy, vemurafenib, have shown. The analysis included patients with advanced melanoma who had a V600 BRAF mutation and who had no previous BRAF-targeted treatment.

Approximately half of all melanomas harbor a V600E mutation in the BRAF gene; in those patients, the nearby MEK pathway is also highly active. While the approval of vemurafenib last year represented a major research achievement, most patients eventually develop resistance to the drug. It is hoped that simultaneously targeting the two active pathways – BRAF and MEK – will provoke a stronger anti-cancer response and prevent, or further delay, treatment resistance.

"It's fascinating to find such promising effects with this combination regimen. Not only are the two drugs causing shrinkage of the cancer, but we're seeing that a second anti-cancer therapy may actually suppress the side effects of the first," said Jeffrey Weber, M.D., Ph.D., a senior member at H. Lee Moffitt Cancer Center and director of the Donald A. Adam Comprehensive Melanoma Research Center.

While the overall trial included 125 patients who received varying doses of dabrafenib and trametinib, the current analysis focuses on a sub-group of 77 patients who received no prior BRAF-targeted therapy (other prior therapies, such as chemotherapy, were permitted), and thus had no prior resistance to BRAF-targeted therapy. Among these 77 patients, median progression-free survival was 7.4 months, which is comparable to what was observed in past single-agent vemurafenib studies. Survival data is expected later this year.

Skin lesions are a well-known side effect of vemurafenib therapy, occurring in up to one-quarter of patients. In this trial, such toxicities were far less common: just 2 percent of the 125 patients in the overall trial developed squamous cell carcinomas and another two percent developed actinic keratoses. Additional common, but manageable, side effects included fever, fatigue and dehydration.

ASCO2012特集

オランザピンは化学療法の副作用をコントロールする（Abstract＃9064）

抗精神病薬は化学療法誘発性悪心･嘔吐をコントロールする

Anti-psychotic drug controls breakthrough chemotherapy-induced nausea and vomiting

従来の治療が奏効しないがん患者の化学療法誘発性悪心・嘔吐（CINV）に関する第3相試験の結果、時に衰弱をもたらすがん治療によるこの副作用に対し、抗精神病薬オランザピンが有効であるとの初めての決定的なエビデンスが示された。第48回American Society of Clinical Oncology学会で発表されたこのスタディにおいて、化学療法治療歴のない患者205人はまずガイドラインの推奨するCINV予防薬を化学療法前に投与された。これらの薬剤は多くの患者においてCINVを予防した一方で、80人においてはブレイクスルーCINVが発現した。これらの患者らはその後オランザピンまたはメトクロプラミドを毎日、3日間内服する群に無作為に割り付けられた。患者は72時間フォローされ看護師からの電話を受けたり日記を記載するよう求められた。72時間の観察期間中にオランザピン投与患者の71%（42人中30人）に嘔吐はなく、メトクロプラミド投与患者におけるその割合は32%（38人中12人）であった。オランザピンを内服した患者の67%は悪心が発現しなかったのに対し、メトクロプラミドにおけるその割合は24%であった。

Full Text

A Phase III trial in cancer patients with chemotherapy-induced nausea and vomiting (CINV) that does not respond to conventional treatments provides the first conclusive evidence that olanzapine, an anti-psychotic medication, is effective in controlling these sometimes debilitating side effects of cancer therapy. The trial was presented at the American Society of Clinical Oncology's 48th Annual Meeting.

Overall, CINV affects about 50 to 60 percent of patients taking certain types of chemotherapy. While these side effects can usually be controlled with available medications, a significant minority of patients, about 30 to 40 percent, experience "breakthrough" CINV, which is defined as nausea and vomiting that persists despite preventive treatment recommended by ASCO or other guidelines.

The double-blind, randomized controlled trial compared olanzapine to metoclopramide, a drug often prescribed for breakthrough CINV although research has not been conducted to confirm its effectiveness for that purpose. Patients who received olanzapine did significantly better than the patients who received metoclopramide.

"This is the first time that breakthrough CINV has been studied in a systematic way," said Rudolph M. Navari, M.D., Ph.D., lead author of the study and professor of medicine, associate dean and clinical director of the Harper Cancer Institute, Indiana University School of Medicine-South Bend. "This study suggests that olanzapine will be very useful in these patients who feel very sick and sometimes come to the clinic, hospital or emergency room. As a result, patients will feel better."

Breakthrough CINV can lower the quality of life for cancer patients and can even necessitate reductions in their chemotherapy doses, possibly limiting the effectiveness of treatment. The study enrolled patients receiving highly emetogenic chemotherapy drugs, including cisplatin, doxorubicin and cyclophosphamide.

In the study, 205 patients who had never received chemotherapy were first given standard guideline-recommended drugs to prevent CINV prior to starting their chemotherapy. While these drugs prevented CINV in most of the patients, 80 patients developed breakthrough CINV. These patients were then randomized to receive either daily oral olanzapine or daily oral metoclopramide for three days. They were followed for 72 hours, through phone calls from study nurses, and were asked to fill out a diary.

During the 72-hour observation period, 71 percent (30 of 42) of those receiving olanzapine had no vomiting, compared to 32 percent (12 of 38) of those receiving metoclopramide. Sixty-seven percent (28 of 42) of the patients taking olanzapine experienced no nausea, compared with24 percent (9 of 38) of those taking metoclopramide.

While olanzapine, approved by FDA for treatment of psychosis, is known to cause a variety of side effects when taken daily for six months or longer, the short-term use in this study did not lead to any significant toxicities. Breakthrough CINV generally develops between the second to fourth days after chemotherapy treatment, so it would not be necessary to take olanzapine for longer than three days, Dr. Navari said. Olanzapine is relatively inexpensive and is taken orally.

ASCO2012特集

限局性高リスク前立腺がんの有望な治療（Abstract # 4521）

術前ホルモン療法にabirateroneを追加することにより一部の高リスク前立腺がん男性の腫瘍が除去しうる

Adding abiraterone to hormonal therapy before surgery can eliminate tumor in the prostate in some men with high risk prostate cancer

第48回American Society of Clinical Oncology学会で発表された無作為化第2相スタディの結果、前立腺全摘術前の標準的なホルモン治療に6か月間の標的治療薬abirateroneを追加することにより、限局性高リスク前立腺がん男性の3分の1においてがんが消失したかまたはほぼ消失したことが示された。このスタディの対象となった男性はPSAレベルが20を超えておりGleasonスコアは8以上でステージT3がんを有していた。過去のスタディの結果、術前のleuprolideを含む標準的なホルモン単独療法の有益性は限られていることが示されている。今回のスタディでは2つのグループの男性（グループAはleuprolideホルモン療法を12週間受けた後にleuprolideとabirateroneをさらに12週間受ける男性27人、グループBはabirateroneおよびleuprolideの両者を24週間受ける男性29人）にabiraterone とleuprolideを追加した。前立腺手術は24週間の治療終了後に全員に対し施行され、組織のがんの所見の有無が調査された。グループBの男性のうち34%は手術の時点で完全消失またはほぼ完全消失していた（p=0.894）。グループAでは手術の時点で15%が完全消失またはほぼ完全消失していた。

Full Text

A randomized Phase II study presented at American Society of Clinical Oncology's 48th Annual Meeting, shows that six months of treatment with the targeted drug abiraterone, in addition to standard hormonal therapy before surgical removal of the prostate, eliminated or nearly eliminated cancer in one-third of men with localized high-risk prostate cancer. The study marks the first time that abiraterone ─ a drug used to treat more advanced prostate cancer ─ has been explored for the treatment of earlier-stages of prostate cancer, including in the neoadjuvant setting.

Localized high-risk disease is generally defined as prostate cancer in men with a PSA level above 20, high-grade disease (a Gleason score of 8 or more), and stage T3 disease. Men with this stage of disease tend to have a poor prognosis, often experiencing cancer spread to other parts of the body despite aggressive treatment with available therapies.

"For this proportion of patients with high-risk disease to have very little to no detectable cancer in the prostate after six months of therapy is dramatic," said Mary-Ellen Taplin, M.D., Associate Professor of Medicine at Harvard Medical School and the Dana-Farber Cancer Institute and the study's lead author. "Our findings suggest that this combination therapy approach could improve outcomes for a substantial number of men, but larger, long-term trials are needed to confirm this approach."

Previous studies have shown that use of standard hormonal therapy alone, including treatment with leuprolide, before surgery had limited benefits for men with localized high-risk prostate cancer. This study evaluated the effect of adding abiraterone to leuprolide in two groups of men with this form of the disease: Group A included 27 men who received leuprolide hormonal therapy for 12 weeks followed by leuprolide plus abiraterone for another 12 weeks. The second group, Group B, included 29 men who received both abiraterone and leuprolide for the entire 24-week period. Prostate surgery was performed in all men after 24 weeks of therapy, and the tissue was examined for evidence of cancer.

Among men in Group B (24 weeks of abiraterone therapy), 34 percent had either complete elimination (3/29) or nearly complete elimination (7/29) of their cancer upon surgery. In Group A (12 weeks of abiraterone therapy), 15 percent of men had either complete elimination (1/27) or nearly complete elimination (3/27) of their cancer upon surgery. Therapy was well-tolerated by both groups.

Abiraterone works by blocking production of the male hormone testosterone and related metabolites that often fuel prostate cancer growth. The addition of abiraterone to traditional hormonal therapy, which restricts testosterone production in a different way, further shuts down the body's ability to produce the hormones that prostate cancer cells need to grow. The clinical benefit of intensive androgen deprivation therapy, either before or after prostatectomy, will need to be validated in prospective, randomized clinical trials, but these data suggest a benefit for some men.

ASCO2012特集

卵巣がんにおける無増悪生存期間の倍加（Abstract＃LBA5002）

プラチナ抵抗性卵巣がんに対する化学療法にベバシズマブを併用することにより無増悪生存期間が改善する

Adding bevacizumab to chemotherapy for platinum-resistant ovarian cancer improves progression-free survival

プラチナ抵抗性卵巣がん女性の第3相無作為化トライアルにおいて、標準的な化学療法にベバシズマブを併用することにより無増悪生存期間（PFS）が倍になったとの結果が第48回American Society of Clinical Oncology学会において発表された。この多施設国際スタディでは、最終のプラチナ製剤投与後6か月以内に増悪を認めた上皮性卵巣がん、卵管がんまたは原発性腹膜がん患者361人に対し、ベバシズマブ併用化学療法と化学療法単独を比較した。全ての患者がこの状況で通常提案される3つの標準的な化学療法—週1回のパクリタキセル、topotecan、またはペグ化リポソームドキソルビシン—のうちのいずれかを受けていた。追跡期間中央値13.5か月後、ベバシズマブ併用化学療法群患者の75%（179人中135人）において再発が認められたのに対し、化学療法単独群患者におけるその割合は91%（182人中166人）であった。PFS中央値は併用群で6.7か月であり、単独群では3.4か月であった。全生存期間に関するデータはまだ出揃っていない。有害事象発現率はベバシズマブ群において高かった。有害事象はグレード2を超える高血圧（20%対7%）、蛋白尿（11%対1%）、消化管穿孔（2%対0）、消化管瘻または膿瘍（2%対0）などであった。

Full Text

Adding bevacizumab to standard chemotherapy doubled progression-free survival (PFS) in a phase III randomized trial of women with platinum-resistant ovarian cancer according to a study presented at the American Society of Clinical Oncology's 48th Annual Meeting.

"These results are very significant because the addition of bevacizumab offers a new treatment option for the 20 percent of women who have primary platinum-resistant disease, as well as those whose disease later becomes platinum-resistant," said lead study author Eric Pujade-Lauraine, M.D., Ph.D., professor, Université de Paris Descartes, France and head of the Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), a clinical trials cooperative group based in France. "For the first time in platinum-resistant ovarian cancer, we have been able to significantly improve progression-free survival with a combination therapy."

The multi-center international randomized study evaluated bevacizumab added to chemotherapy vs. chemotherapy alone in 361 patients with epithelial ovarian, fallopian tube or primary peritoneal cancer with disease progression within six months of their last dose of platinum therapy. All patients received one of three standard chemotherapy drugs normally offered in this setting—weekly paclitaxel, topotecan or liposomal pegylated doxorubicin. These treatments are equally effective in treatment for resistant ovarian cancer, differing only in their toxicities. The investigators selected the chemotherapy based on each patient's previous experience with the drugs.

After a median follow-up of 13.5 months, 75 percent (135 of 179) of the patients who received bevacizumab in addition to chemotherapy had a recurrence, compared to 91 percent (166 of 182) who received chemotherapy alone.

Median PFS was 6.7 months in the combination group, compared to 3.4 months in the chemotherapy alone group. Overall survival data is not yet complete.

Adverse events were higher in the bevacizumab group. These included greater than Grade 2 hypertension (20 percent vs. 7 percent), proteinuria (11 percent vs. 1 percent), gastrointestinal perforations (2 percent vs. 0), and fistula or abscesses (2 percent vs. 0). For other adverse events greater than Grade 3, the study arms were equivalent.

Strict patient selection—based on the absence of history of bowel obstruction/abdominal fistula or clinical/radiological evidence of rectosigmoid involvement—helped to limited the incidence of adverse events due to bevacizumab, Dr. Pujade-Lauraine said.

Previous studies have shown that bevacizumab is active in first-line and second-line treatment of ovarian cancer. Future studies are likely to test when and how long to treat the disease with this agent.

ASCO2012特集

リンパ腫の新たな治療法はCHOPよりも有効性が高い（Abstract＃3）

リンパ腫に対するベンダムスチン療法は標準的な治療法よりも有効性が高く副作用が少ない

Bendamustine regimen more effective for lymphoma than standard therapy with fewer side effects

第48回American Society of Clinical Oncology学会で発表された多施設第3相試験の結果、緩徐進行性リンパ腫およびマントル細胞リンパ腫患者において、bendamustineとリツキシマブによる併用化学療法は標準治療よりも無増悪生存期間を倍の6年近くにまで延長することが示された。研究者らは未治療の緩徐進行性非ホジキンリンパ腫またはマントル細胞リンパ腫患者514人を、ベンダムスチン/リツキシマブ（B-R）またはリツキシマブとシクロホスファミド、ドキソルビシン、ビンクリスチンおよびプレドニゾロン（R-CHOP）のいずれかを投与される群に無作為に割り付け、無増悪生存期間を比較した。追跡期間中央値45か月後の無増悪生存期間（PFS）中央値は、B-R群で69.5か月であったのに対しR-CHOP群では31.2か月であった。全生存期間は両群間で差がなく、その理由の一部は疾患が増悪し続けたR-CHOP患者の半数はB-Rを受けることを許可されたためであり、一部は緩徐進行性リンパ腫の生存期間は非常に長い傾向にあるためであった。そのためPFSが最も信頼できる臨床上の有益性や患者のQOLの指標となっている。Bendamustine療法は副作用も少なかった。

Full Text

Long-term results from a multicenter Phase III study presented at the ASCO's 48th Annual Meeting show that initial combination chemotherapy with bendamustine and rituximab more than doubled progression-free survival, to nearly six years, compared with standard R-CHOP therapy among patients with indolent lymphoma and mantle cell lymphoma. The bendamustine regimen was also associated with fewer side effects.

"This is the first randomized clinical trial to compare bendamustine and rituximab with a standard chemotherapy regimen for these more challenging types of lymphoma, and it clearly shows that the bendamustine-based regimen is more effective and less toxic," said Mathias J. Rummel, M.D., Ph.D., Professor of Medicine at the University Hospital Giessen in Germany and lead author of the study. "Just as important, bendamustine-based therapy allowed patients to have a better quality of life while undergoing therapy. These long-term findings should be strong enough to change clinical practice."

R-CHOP, a standard chemotherapy regimen for many non-Hodgkin lymphomas, includes the targeted therapy rituximab plus the drugs cyclophosphamide, doxorubicin, vincristine and prednisone. Bendamustine has been used for decades in Europe (it was developed in Eastern Europe), but only became available in the U.S. in 2008. While many U.S. doctors already use the bendamustine-based regimen based on earlier data from this trial, uptake has not been universal.

The investigators compared progression-free survival between 514 patients with previously untreated indolent non-Hodgkin or mantle cell lymphomas who were randomly assigned to receive either bendamustine/rituximab (B-R) or R-CHOP. After a median follow-up of 45 months, median progression-free survival (PFS) was 69.5 months in the B-R group versus 31.2 months for the R-CHOP group. Overall survival did not differ between the two groups, partly because nearly half of the R-CHOP patients whose disease continued to progress were then permitted to receive B-R, and partly because survival for indolent lymphomas tends to be very long, making PFS the most reliable measure of clinical benefit and patient quality of life.

While there was a higher incidence of mild skin reactions in the B-R group, there was no hair loss and a lower incidence of nerve toxicity and infections, compared with the R-CHOP group. Moderate to severe declines in neutrophil counts (a type of white blood cell) occurred in 69 percent of the R-CHOP patients and 29 percent of the B-R group; G-CSF treatment (a drug used to boost neutrophil counts) was needed after 20 percent of R-CHOP chemotherapy cycles, but after only 4 percent of B-R cycles.

ASCO2012特集

進行肺がんの進行抑制（Abstract＃LBA7500）

LUX-lung 3トライアル:Afatinibは進行肺腺がん、特に一部の遺伝子サブセットの腫瘍において進行を遅らせる

LUX-lung 3 trial: Afatinib delays progression of advanced lung adenocarcinomas, particularly in genetic subset of tumors

第48回American Society of Clinical Oncology学会で発表された第3相国際トライアルの結果、分子標的薬afatinibを用いた初回単剤経口療法は、上皮細胞増殖因子受容体(EGFR、ErbB1としても知られる)変異を有する進行肺腺がん患者の無増悪生存期間(PFS)を延長させることが示された。このスタディにおいて研究者らは345人の患者をafatinibまたは経静脈投与による標準的な併用化学療法に無作為に割り付けた。LUX-lung 3トライアルの患者全員が中央検査でEGFR変異を有することが同定され、画像検査は個々に読影され治療の結果を評価された。追跡期間中央値8か月後に、afatinibは疾患の増悪を標準治療よりも4か月延長した（PFS:11.1対6.9か月）。19またはL858Rの欠失を有する患者308人においては、PFSはさらに長かった（13.6対6.9か月）。Afatinibによる治療を受けた患者はまた、標準的な化学療法を受けた患者と比較し、咳や呼吸困難などの肺がんに伴う一般的な症状の悪化が遅く、QOLが良好であった。Afatinibによる副作用はEGFR標的治療と同等であった。全生存期間に関するデータは2年以内に得られる予定である。

Full Text

Results from a Phase III international trial presented at ASCO's 48th Annual Meeting show that initial single-agent oral therapy with the targeted drug afatinib prolongs progression-free survival (PFS) in patients with advanced lung adenocarcinomas that harbor epidermal growth factor receptor (EGFR, also known as ErbB1) mutations, compared with standard chemotherapy. Researchers found that afatinib was particularly beneficial – leading to a doubling of PFS – in the majority of patients who had one of two common types of EGFR mutations, deletion 19 or L858R. These two mutations together account for approximately 90 percent of all EGFR mutations.

This is the first time findings from this trial – LUX-lung 3 – have been presented, and they are of particular interest because researchers compared afatinib with a relatively new first-line regimen for advanced, previously untreated lung adenocarcinoma: combined pemetrexed and cisplatin chemotherapy. This form of disease is a subtype of non-small cell lung cancer. EGFR mutated, or driven, lung adenocarcinoma is often clinically associated with patients who have never smoked and patients of Asian descent.

The EGFR pathway facilitates cancer cell growth, survival and spread. Laboratory studies have shown that afatinib chemically blocks this pathway more thoroughly and permanently than current EGFR-targeted treatments, such as gefitinib and erlotinib. Additionally, afatinib blocks the broader ErbB family of receptors that are associated with the EGFR pathway, including HER2 (ErbB2) and HER4 (ErbB4), and can inactivate further cancer cell pathways.

"By more broadly and effectively blocking the molecular pathways that facilitate the growth of these cancers, afatinib appears to be more potent than other therapies," said James Chih-Hsin Yang, M.D., Ph.D., a Professor at the National Taiwan University and the principle investigator of this multi-national study. "This new treatment could not only help patients live a longer period of time without further cancer progression, but because it's given orally, it may also require fewer visits to the doctors' office than standard chemotherapy – another important quality of life advantage."

In this study, researchers randomized 345 patients to afatinib or standard combination chemotherapy treatment, given intravenously. All participants had EGFR mutations that were identified through central testing, and the imaging scans were independently reviewed to evaluate treatment outcomes. After a median follow-up of 8 months, they found that afatinib delayed disease progression by more than 4 months over standard therapy (PFS: 11.1 vs. 6.9 months). Among the 308 patients with either deletion 19 or L858R, PFS was prolonged even further (13.6 vs. 6.9 months). Researchers noted that patients treated with afatinib were also slower to experience worsening of common lung cancer-related symptoms, including cough and dyspnea and showed a better quality of life when compared with patients receiving chemotherapy.

Side effects with afatinib were comparable to those of other EGFR-targeting therapies. Overall survival data are expected in about two years, according to Dr. Yang.

ASCO2012特集

Trametinibは進行メラノーマの生存期間を改善する（Abstract # LBA8509）

METRIC study:新たなMEK阻害薬は進行BRAF-変異メラノーマ患者の生存期間を改善する

METRIC study: New MEK inhibitor improves survival for patients with advanced BRAF-mutated melanoma

第48回American Society of Clinical Oncology学会で発表された第3相試験のデータから、経口治験薬が標準的な化学療法と比較し、BRAF変異を有する進行メラノーマ患者の腫瘍増殖を遅延させ生存期間を延長させることが示された。METRICとして知られるこのスタディにおいて、最高1回の化学療法を受けたことのある進行BRAF変異メラノーマ患者をtrametinib（214人）または標準的な化学療法（108人；dacarbazineまたはパクリタキセル）を受ける群に無作為に割り付けた。全体で、trametinib治療を受けた患者の22%が治療に奏効したのに対し化学療法群患者でのそれは8%であった。無増悪生存期間中央値はtrametinib投与群（4.8か月）の方が化学療法群（1.5か月）よりも有意に長かった—増悪リスクは55%低下した。中間全生存期間もまたtrametinib治療群で有意に長く、死亡リスクは46%低下した；6か月後に生存していたのはtrametinib群患者で81%であったのに対し、化学療法群では67%であった。化学療法中に疾患が増悪した患者のほぼ半数（47%）はtrametinib内服を許可されたため、全生存期間に関する有益性はこの“クロスオーバー効果”を考慮するとさらに大であることが最終的に証明されるであろう。

Full Text

Data from a Phase III study presented at the American Society of Clinical Oncology's 48th Annual Meeting show that the oral investigational drug trametinib delayed tumor growth and extended survival for patients with advanced melanoma who have BRAF mutations, compared with standard chemotherapy. This is the first Phase III trial evaluating a melanoma treatment that inhibits a protein known as MEK ─ part of the MAP kinase-signaling pathway, of which BRAF is also a component.

"This is the first in a new class of targeted drugs that could benefit patients with melanoma who have BRAF mutations. The findings show that targeting the MEK molecular pathway is a viable strategy for treating many people with the disease," said Caroline Robert, M.D., Ph.D., Head of Dermatology at the Institute Gustave Roussy in Paris, France. "Trametinib is likely to become another first-line treatment option for patients with advanced melanoma."

Only one targeted therapy, vemurafenib, is currently approved for advanced melanoma. Vemurafenib targets a protein produced by a mutation in the BRAF gene that fuels melanoma growth, and is present in roughly half of patients with melanoma. MEK lies downstream from BRAF in the same signaling pathway. Since most patients taking vemurafenib eventually develop resistance to the drug and many experience serious side effects, MEK inhibitors could help address a continuing need for new therapies in these patients.

In this study, known as METRIC, patients with advanced BRAF-mutated melanoma who had received up to one prior chemotherapy regimen were randomly assigned to receive trametinib (214 patients) or standard chemotherapy (108 patients; either dacarbazine or paclitaxel). Overall, 22 percent of patients who received trametinib responded to treatment, compared with 8 percent of those who received chemotherapy.

Median progression-free survival was significantly greater in the trametinib group (4.8 months) than the chemotherapy group (1.5 months) – a 55 percent reduction in the risk of progression. Interim overall survival was also longer among the patients treated with trametinib, with a 46 percent reduced risk of death; 81 percent of patients in the trametinib group were alive after six months of follow-up, versus 67 percent in the chemotherapy group. Approximately half (47 percent) of patients whose disease progressed while on chemotherapy were permitted to take trametinib, so the overall survival advantage may ultimately prove to be greater if this "crossover effect" is taken into account, according to the researchers.

Side effects of trametinib were generally manageable. Severe adverse events included skin rash (7 percent of patients), eye problems (less than 1 percent), high blood pressure (12 percent) and reduced heart function (7 percent).

ASCO2012特集

スタディにより前立腺がんに関する論争が決着した（Abstract＃4）

一部の進行前立腺がん男性において間欠的なホルモン療法は持続的なホルモン療法よりも有効性が低い

Intermittent hormonal therapy less effective than continuous therapy in certain men with advanced prostate cancer

ホルモン感受性転移前立腺がん男性に対する2つの一般的な治療法を比較した長期多施設第3相国際臨床試験の結果、転移が最小限の患者において間欠的なホルモン療法は持続的なホルモン療法よりも有効性が低いことが示された。このトライアルには、7か月間の持続的なホルモン療法の後にPSAが4ng/mL以下に低下したホルモン感受性転移性前立腺がん男性1,500人余りを組み入れた。その後彼らは間欠的ホルモン療法（770人）または持続的ホルモン療法（759人）を受ける群に無作為に割り付けられた。間欠的治療群患者は定期的に治療を受けたため、この群の患者は平均で持続的治療群患者の半分のホルモン療法を受けた。追跡期間中央値9.2年後にがんの転移が最小限（転移が脊椎、骨盤、およびリンパ節を越えない）の患者の全生存期間中央値は、持続的治療群で7.1年であったのに対し、間欠的治療群では5.2年であった。がんがより広範に転移している患者においては、全生存期間中央値は両群で同等であった（持続的治療群で4.4年に対し間欠的治療群で5年）。このスタディは第48回American Society of Clinical Oncology学会で発表された。

Full Text

A long-term, multicenter Phase III international clinical trial comparing two common therapies for men with hormone-sensitive metastatic prostate cancer has found that intermittent hormonal therapy is less effective than continuous hormonal therapy in men with minimal disease spread. There was a two-year difference in median survival among these men, favoring men who received continuous therapy. Among men with more extensive disease spread, however, the results indicate that intermittent and continuous therapy are comparably effective. The study was presented at the American Society of Clinical Oncology's 48th Annual Meeting.

"Some doctors recommend intermittent hormonal therapy to men with metastatic prostate cancer, believing it will reduce their risk of side effects without compromising their outcome, but these findings demonstrate a clear downside to this approach for certain men," said Maha Hussain, M.D., Professor of Medicine and Urology at the University of Michigan Comprehensive Cancer Center and the study's lead author. "The findings clearly demonstrate that intermittent hormonal therapy is not safe for all patients with metastatic prostate cancer. They will be practice changing for many doctors in the U.S. and abroad who routinely use intermittent therapy."

Prostate cancer is fueled by the male hormone testosterone; hormonal therapy is used to turn off testosterone production and thereby stop cancer growth. But hormonal therapy has side effects that impair quality of life, including reduced sexual drive and potency, hot flashes and weight gain. Based on early scientific and clinical data, doctors have thought for some time that intermittent hormonal therapy could decrease these side effects and perhaps delay the resistance to hormonal therapy that most metastatic prostate cancers develop.

Intermittent hormonal therapy appeared to be safe in prior studies, but those studies generally included either men whose only evidence of prostate cancer progression was an increase in PSA level (as opposed to X-ray evidence of disease spread, for example), or men with wide-ranging stages of disease (not just metastatic cancer).

This National Cancer Institute-sponsored intergroup study (led by SWOG) was designed to see if intermittent hormonal therapy achieved survival comparable with continuous therapy among men with metastatic prostate cancer. The trial included more than 1,500 men with hormone-sensitive metastatic prostate cancer whose PSA fell to 4 ng/ml or less after 7 months of continuous hormonal therapy. The men were then randomly assigned to receive intermittent hormonal therapy (n=770 patients) or continuous hormonal therapy (n=759 patients). Because treatment was given periodically, patients in the intermittent therapy group received, on average, about half as much hormonal therapy as those in the continuous therapy group.

After a median follow-up of 9.2 years, median overall survival in men with minimal disease spread (no spread beyond the spine, pelvis, and lymph nodes) was 7.1 years for those who received continuous therapy versus 5.2 years for those who received intermittent therapy. Among men with more extensive disease spread, median overall survival was similar in both arms (4.4 years for the continuous therapy group vs. 5 years for the intermittent group).

ASCO2012特集

新たな分子標的薬はGIST患者の予後を改善する（Abstract # LBA10008）

Regorafenibは承認標的治療に対する耐性のために進行した消化管間質腫瘍に対し有効である

Regorafenib effective for gastrointestinal stromal tumors that progress due to resistance to approved targeted therapies

第48回American Society of Clinical Oncology学会で発表された第3相国際トライアルの結果、新たな経口分子標的薬regorafenibは、イマチニブやスニチニブを含む他の使用可能な治療オプションに対する耐性のために進行した消化管間質腫瘍（GIST）患者の予後を改善しうることが示された。研究者らは転移性および/または手術不能なGIST患者199人をregorafenibまたはプラセボと疾患の症状を緩和する最良の支持療法を併用する群に無作為に割り付けた。全ての患者が過去に少なくとも標準的なイマチニブおよびスニチニブ療法を受けていた。その結果、無増悪生存期間はregorafenibを用いて治療された患者（4.8か月）においてプラセボを用いた患者（0.9か月）よりも4倍長かった。疾患が悪化した場合にはプラセボ群患者はregorafenib治療に変更することが許可されていた；全体で85%の患者がregorafenib内服に変更することができた。このトライアルデザインのために、全生存期間は両群間で統計学的な差を認めなかったが、治療の過程でregorafenibを早期に開始した患者において有意ではないが好ましい傾向がみられた。この薬剤の忍容性は全般的に良好で、副作用はGISTに対する他の承認分子標的薬と同等であった。

Full Text

Results of an international Phase III trial presented at the American Society of Clinical Oncology's 48th Annual Meeting demonstrate that the new targeted oral drug, regorafenib, can improve outcomes for patients with gastrointestinal stromal tumors (GIST) that progress due to resistance to other available treatment options, including imatinib and sunitinib.

The researchers found that progression-free survival was four times longer among patients receiving regorafenib than among those receiving placebo. All patients also received best supportive care to alleviate the symptoms of their disease.

"If approved, regroafenib will fulfill an urgent unmet need for patients with GIST who have exhausted all other treatment options," said George Demetri, M.D., Director of the Ludwig Center and Sarcoma Center at Dana-Farber Cancer Institute and Harvard Medical School in Boston. "Targeted therapy has revolutionized treatment for this rare cancer, but we've been on the hunt for additional effective treatments for the 85 percent of patients whose cancer eventually develops resistance to the only two available therapies. Regorafenib appears to target GIST tumors in a different and possibly more powerful way than the current FDA-approved therapies, making it a potentially significant new option to help patients."

Like other approved "smart drugs" for GIST, regorafenib targets abnormalities in cancer cell signaling pathways driven by an enzyme called KIT. Although initially suppressed by targeted therapies such as Gleevec, new mutations eventually evolve which lead to drug-resistant forms of the KIT enzyme, allowing the cancer to grow despite continuing the drugs which initially worked. Regorafenib appears to inhibit the cancer-promoting signals in a unique way, working even in patients whose cancers have developed resistance to the other treatments.

In this study, researchers randomized 199 patients with metastatic and/or inoperable GIST patients to either regorafenib or placebo plus best supportive care. All had undergone prior treatment with at least standard imatinib and sunitinib therapy. Progression-free survival was significantly longer among patients treated with regorafenib (4.8 months), compared with placebo (0.9 months). If the disease worsened, patients on placebo were allowed switch to regorafenib treatment; in all, 85 percent of patients were able to cross over to receive regorafenib. Because of this trial design, there was no statistical difference in overall survival between the two arms, although a non-significant trend was noted in favor of patients who started regorafenib earlier in the course of care. The drug was well-tolerated overall, with side effects similar to other approved targeted agents for GIST.

ASCO2012特集

進行乳がんに関する新たな治療法は有望である（Abstract＃LBA1）

EMILIA:HER2-陽性進行乳がんの新たな治療法は現在の標準治療よりも無増悪生存期間を延長させる

EMILIA: New treatment for HER2-positive advanced breast cancer, improves progression-free survival over current standard therapies

治験薬トラスツズマブ-DM1（T-DM1）をカペシタビンとラパチニブ（XL）を用いた標準治療と比較した第3相無作為化スタディの結果、タキサンとトラスツズマブ治療歴を有するHER2陽性局所進行または転移性乳がん患者においてT-DM1による有意かつ臨床的に重要な無増悪生存期間（PFS）の改善が示された。EMILIAと呼ばれるこの国際スタディでは1,000人近くの患者をT-DM1またはXLを疾患が増悪するかまたは対処不能な毒性が出現するまで3週ごとに施行する群に無作為に割り付けた。PFS中央値はT-DM1治療群で9.6か月であったのに対し、XL群では6.4か月であった―この差は統計学的に有意であった。2年後の生存率はT-DM1群で65.4%であったのに対し、XL群では47.5%であった。この統計的有意性における差はトライアルであらかじめ定義された一次解析用の統計学的生存率閾値に合致しなかった。スタディ後半で計画されている二次生存解析により、さらなる情報が提供されるであろう。T-DM1群におけるグレード3以上の一般的な有害事象は血小板減少（12.9%対0.2%）および肝機能検査値上昇であった。これらの副作用は休薬期間を設けることにより解決した。このスタディは2012年ASCO学会で発表された。

Full Text

A phase III randomized study of the investigational agent trastuzumab emtansine (T-DM1) vs. standard therapy using capecitabine and lapatinib found significant and clinically meaningful improvement in progression-free survival (PFS) for T-DM1 in women with HER2-positive locally advanced or metastatic breast cancer previously treated with a taxane and trastuzumab. Results were presented at the American Society of Clinical Oncology's 48th Annual Meeting.

T-DM1 is an experimental antibody-drug conjugate that consists of the antibody trastuzumab linked to the cytotoxic drug emtansine (DM1).

"The drug worked. It was significantly better than a very effective approved therapy for HER2 overexpressing metastatic breast cancer," said lead study author Kimberly L. Blackwell, M.D., professor of medicine and assistant professor of radiation oncology at Duke Cancer Institute at Duke University. "Also, as a clinician who takes care of a lot of breast cancer patients, I'm pleased that this drug has very little dose-limiting toxicity. Patients don't lose their hair from this drug. For patients facing metastatic breast cancer, this is a breakthrough."

The international study, called EMILIA, randomized nearly 1,000 patients to receive either T-DM1 or XL every three weeks until their disease progressed or they experienced unmanageable toxicity.

The median PFS for patients receiving T-DM1 was 9.6 months, compared to 6.4 months in the group receiving capecitabine and lapatinib (a regimen known as XL) – a difference that was statistically significant.

After two years, 65.4 percent of the T-DM1 patients were alive, compared to 47.5 percent of the XL patients. This difference in statistical significance did not meet the trial's predetermined statistical survival threshold for the first analysis. The second survival analysis planned for later in the study will provide additional information.

The most common adverse events of Grade 3 or above for T-DM1 included thrombocytopenia (12.9 percent vs. 0.2 percent) and elevation in liver function tests. These side effects resolved when patients took a break from the drug, Dr. Blackwell said. Dose reductions were greater for patients in the XL group: 53.4 percent for capecitabine, 27.3 percent for lapatinib, and 16.3 percent for T-DM1.

Patients in the XL group experienced more diarrhea (20.7 percent vs. 1.6 percent), hand-foot syndrome (16.4 percent vs. 0), and vomiting (4.5 percent vs. 0.8 percent).

ASCO2012特集

進行大腸がん患者の生存期間延長（Abstract＃CRA3503）

進行大腸がん初回増悪後のセカンドライン化学療法にベバシズマブを継続することにより生存期間が延長する

Continuing bevacizumab with second-line chemotherapy after first progression extends survival for advanced colorectal cancer

第48回American Society of Clinical Oncology学会で発表された大規模第3相臨床試験の結果、ファーストラインとしてベバシズマブ併用療法を受けた進行大腸がん患者のセカンドラインとしての標準的な化学療法とベバシズマブによる併用療法が全生存期間を延長したことが示された。この第3相無作為化トライアルでは、転移性の切除不能大腸がん患者820人が標準的なファーストライン化学療法（医師の選択によりオキサリプラチンまたはイリノテカンベース）とベバシズマブの併用で治療された。疾患増悪を受けて、患者はもう片方の化学療法薬とベバシズマブまたはプラセボ併用群に無作為に割り付けられた。その結果、全生存期間（11.2か月対9.8か月）および無増悪生存期間（5.7か月対4.1か月）は、ベバシズマブ投与群において有意に長かった。全体的に両群患者とも治療の忍容性は良好であった：ベバシズマブによる副作用は過去のスタディで認められたものと同等であった。これはファーストラインとしてベバシズマブ併用療法を受けた患者に対するセカンドライン治療としてのベバシズマブ継続併用療法を評価した、はじめての無作為化トライアルである。

Full Text

Results from a large, Phase III clinical trial presented at the American Society of Clinical Oncology's 48th Annual Meeting show that combination treatment with bevacizumab and standard chemotherapy in the second line setting in patients with advanced colorectal cancer who have received bevacizumab combination treatment first-line extends overall survival.

"These findings confirm what many physicians and researchers have long suspected – that extended bevacizumab treatment provides meaningful benefits for patients with advanced colorectal cancer, without adding significant side effects," said Dirk Arnold, M.D., Director of the Hubertus Wald Tumor Center, University Cancer Center (UCCH) of University Clinic Eppendorf, Hamburg, Germany, and Speaker of the German AIO Colorectal Cancer Collaborative Study Group (which initiated the trial). "But the findings also provide an important new insight about the biology of advanced colorectal cancer, showing us that if the disease develops resistance to chemotherapy, it does not necessarily mean that tumors become resistant to anti-angiogenic therapy. By simply switching chemotherapy drugs when the cancer progresses and continuing with bevacizumab, we can make second-line treatment even more powerful. This finding will likely spur research into other cancer types that are sensitive to both bevacizumab and chemotherapy."

Bevacizumab is known as an anti-angiogenic targeted therapy. This is the first randomized trial to evaluate the combination regimen in second-line in patients who have previously been treated with a bevacizumab regimen in the first-line setting.

In this Phase III randomized trial, 820 patients with metastatic, inoperable colorectal cancer were treated with standard first-line chemotherapy (physician's choice of oxaliplatin- or irinotecan-based) plus bevacizumab. Following disease progression, patients were randomized to receive the opposite chemotherapy drug plus bevacizumab or placebo. Researchers observed that both overall survival (11.2 months vs. 9.8 months) and progression-free survival (5.7 vs. 4.1 months) were significantly longer among patients who received bevacizumab.

Overall, treatment was well-tolerated by patients in both arms: side effects associated with bevacizumab therapy were comparable with those observed in past studies.

ASCO2012特集

新たな微小管阻害薬は週1回のパクリタキセルと変わりない（Abstract＃CRA1002）

局所進行または転移性乳がん治療において新たなより高価な薬剤は標準的な週1回のパクリタキセル投与と変わりない

Newer, more costly drugs no better than standard weekly paclitaxel for locally advanced or metastatic breast cancer

第48回American Society of Clinical Oncology学会で発表された第3相無作為化トライアルの結果、局所進行または転移性乳がんに対するファーストライン治療として、新たなより高価な2つの薬剤であるnab-パクリタキセルおよびixabepiloneの週1回投与はいずれも標準的な週1回のパクリタキセル投与よりも優れてはいないことが明らかにされた。さらに、この条件下ではパクリタキセルを使用した方がixabepiloneよりも無増悪生存期間（PFS）が長くnab-パクリタキセルよりも毒性が少ないようであった。スタディには799人の患者を組み入れ、これらの3つの治療法のいずれかを受ける群に無作為に割り付けた。PFS中央値はパクリタキセル投与群で10.6か月、nab-パクリタキセル群で9.2か月であり、ixabepilone群で7.6か月であった。週1回のixabepilone投与はパクリタキセルよりも有意に有効性が低く、nab-パクリタキセルもまたパクリタキセルよりも優れてはいなかった。感覚神経障害（パクリタキセル群16%対治験薬群25%）を含むグレード3または4の非血液毒性もまたパクリタキセル群において最も少なかった。グレード3または4の血液毒性はixabepilone群で最も少なくnab-パクリタキセル群で最も多く（12%対51%）、それと比較してパクリタキセル群では21%であった。実際問題として、多くの患者は週1回のパクリタキセル投与により、副作用は少なく低コストで（新たな治験薬を投与された患者と）同等に軽快することがこの結果から示唆された。

Full Text

A phase III randomized trial presented at the American Society of Clinical Oncology's 48th Annual Meeting found that weekly administration of either of two newer and significantly more costly agents, nanoparticle albumin bound ("nab") paclitaxel and ixabepilone, was not superior to standard weekly dosing of paclitaxel as first-line therapy for locally advanced or metastatic breast cancer. Furthermore, paclitaxel appears to offer better progression-free survival (PFS) than ixabepilone and fewer toxicities than nab-paclitaxel in this setting.

In practical terms, the findings suggest that many patients could do equally well on weekly paclitaxel with fewer side effects and at lower cost.

"We wanted to know whether giving these newer microtubule agents when given on a weekly schedule would result in similar or superior effectiveness with improved toxicity profiles over the standard weekly paclitaxel regimen," said lead study author Hope S. Rugo, M.D., professor of medicine and director of breast oncology and clinical trials education at the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA. "This study demonstrates that we should not simply assume that newer drugs are always better than the standard therapies. In metastatic breast cancer, we are constantly examining and refining dosing schedules, testing new therapies, and looking closely at molecular characteristics of patients' tumors to find the right treatment for the right patient, with the fewest toxicities."

The study enrolled 799 patients who were randomized to receive one of the three therapies—paclitaxel, nab-paclitaxel or ixabepilone—on a weekly basis with each cycle consisting of three weeks of treatment followed by a one-week break. The majority of patients enrolled in this trial received bevacizumab.

Median PFS was 10.6 months for those receiving paclitaxel, 9.2 months for nab-paclitaxel, and 7.6 months for ixabepilone. Weekly ixabepilone was significantly less effective than paclitaxel, and nab-paclitaxel was also not superior to paclitaxel. Grade 3 or 4 non-hematologic toxicities were also lowest in the paclitaxel arm, including sensory neuropathy (16% versus 25% for both experimental arms). Grade 3 or 4 hematologic toxicities were lowest in the ixabepilone arm, and highest in the nab-paclitaxel arm (12% versus 51%), compared to paclitaxel (21%). Coupled with the lack of superiority for the newer agents, this suggests that eligible patients can be appropriately treated with paclitaxel using a weekly schedule. Paclitaxel, nab-paclitaxel and ixabepilone are approved by the Food and Drug Administration for metastatic breast cancer.

The study also was designed to look at specific biologic features to understand which patients might benefit the most from one or another of the therapies, and which patients are more susceptible to peripheral neuropathy, a painful side effect of treatment. Investigators await the outcome of these correlative studies in the hopes of better defining which patients might do better on different agents or using different dosing schedules. The newer agents may offer lower toxicity or improved efficacy for some patients, based on molecular characteristics of tumors, but further studies looking at pre-determined patient subsets would be needed.

ASCO2012特集

若年の白血病患者は成人よりも予後が良好である（Abstract＃CRA9508）

青年期および若年成人期の白血病患者はそれより若年の患者よりも再発率が高く生存率が低い

Adolescent and young adult leukemia patients have higher rates of relapse and lower survival than younger patients

高リスク急性リンパ性白血病（HR-ALL）の青年期および若年成人期（AYA）患者（16～30歳）の予後は、若年患者（1～15歳）よりも不良であり、無イベント生存率および全生存率が低かったとのALL治療に関する第3相試験の結果が第48回ASCO学会で発表された。ハイリスクB前駆細胞性ALLに対する4つの治療法を調べたこの無作為化トライアルは、AYA患者501人（16～21歳466人および22～30歳35人）を対象とし、1つのがん臨床試験ではこの年代のこれまでで最大のコホートであった。AYA患者はトライアル全体の組み入れ数2,574人の20%を占めた。5年無イベント生存率はAYA患者で68%であったのに対し、若年患者では80.9%であった。全生存率（OS）はAYA患者で79.8%であり、若年患者では88.4%であった。AYA患者は再発率が高く21.3%であり、若年患者ではその割合は13.4%であった。これらの差は統計学的に有意であった。この結果は、この高年齢層患者の白血病コントロールを改善し、治療毒性を軽減させる新たな戦略の必要性を示している。

Full Text

Adolescent and young adult (AYA) patients (ages 16 to 30) with high risk acute lymphoblastic leukemia (HR-ALL) had poorer outcomes than younger patients (ages 1 to 15), with lower rates of both event-free survival and overall survival, in a major phase III study of ALL treatment presented at the American Society of Clinical Oncology's 48th Annual Meeting. The findings point to the need for new strategies to improve leukemia control and lower treatment toxicity for this older age group.

The randomized trial tested four treatment regimens for high-risk B-precursor ALL. The treatment outcome data based on treatment regimen were presented at the 2011 ASCO Annual Meeting. This year, the investigators report on event-free survival and overall survival of AYA patients compared to younger patients.

Although there is historical data that suggests that AYA patients with HR-ALL have inferior outcome, to date there has not been a trial with substantial numbers of patients who received the same treatment to make a direct comparison, said lead study author Eric Larsen, MD, medical director of the Maine Children's Cancer Program and Study Chair of the Children's Oncology Group protocol AALL0232.

"This study tells us that the inferior outcome for AYA patients is the result of more resistant disease, resulting in higher rates of relapse and higher toxicity from treatment," Dr. Larsen said. "We have to find novel agents to better eradicate the leukemia, but while we want to intensify therapy, we also have to reduce toxicity."

The study included 501 AYA patients, the largest cohort of this age group to date in a single cancer clinical trial. There were 466 patients age 16 to 21 and 35 patients aged 22 to 30. The AYA patients made up 20 percent of the overall trial enrollment of 2,574. Historically pediatric leukemia studies cut off enrollment at age 18, but this trial was designed to include young adults up to age 30.

Five-year event-free survival—defined as having no evidence of disease—was 68 percent in the AYA patients compared to 80.9 percent in the young patients. Overall survival (OS) was 79.8 percent in the AYA patients compared to 88.4 percent in the younger patients. These differences were highly statistically significant.

AYA patients had a higher rate of relapse, 21.3 percent, compared to 13.4 percent for younger patients. This was also statistically significant. The relapses were primarily due to a higher rate of bone marrow relapse in the AYA patients, rather than central nervous system relapse. The treatment strategy of the trial was to try to improve disease control in the central nervous system. There was no statistically significant difference in CNS relapse between AYA and younger patients.

Toxic deaths that occurred after induction therapy and remission were significantly higher in the AYA patients—5.5 percent vs. 2.1 percent.

As a result of this study, the Children's Oncology Group is considering several options to both enhance leukemia control and also reduce the toxicity of treatment. It is hoped that future strategies will continue to improve the outcome for AYA patients with HR-ALL.

ASCO2012特集

化学療法と放射線療法の併用は一部の脳腫瘍患者の寿命を延長する（Abstract＃2）

化学-放射線療法の併用は退形成性乏突起膠腫、特に染色体突然変異を有する者の生存期間を延長する

Combined chemo-radiation extends survival in patients with anaplastic oligodendroglial tumors, particularly those with chromosomal mutations

European Organization for Research and Treatment of Cancer（EORTC）が施行し2012年ASCO学会で発表された第3相試験の結果、脳腫瘍の一種である退形成性乏突起膠腫患者に標準的な放射線治療を行った後に化学療法を併用することにより、腫瘍の成長が遅延し寿命が延長したことが示された。このスタディに登録された患者368人は新たに診断された未治療の退形成性乏突起膠腫を有していた。患者は放射線療法単独または放射線療法の後にPCVとして知られるプロカルバジン、CCNUおよびビンクリスチンを用いた化学療法を6サイクル併用する群に無作為に割り付けられた。今日、この疾患のほとんどの患者が化学療法かまたは放射線療法により治療され、併用療法はなされていない。無増悪生存期間は放射線/PCV療法群で24.3か月であり、放射線療法単独群では13.2か月であった。全生存期間は放射線/PCV療法群で42.3か月であり放射線療法単独群では30.6か月であった。遺伝子サブタイプによる調査を行ったところ、PCVと放射線療法の有益性は1p/19q共欠失を有することが判明しているサブセットの80人に限定された。これらの患者においては放射線/PCV療法により放射線療法単独を受けた患者と比較し、死亡リスクが44%低下した。

Full Text

A Phase III study conducted by the European Organization for Research and Treatment of Cancer (EORTC) and presented at ASCO's 2012 annual meeting has shown that giving combination chemotherapy after standard radiation therapy delayed tumor growth and extended the lives of patients with anaplastic oligodendroglial tumors, a form of brain cancer. A sub-analysis of the study showed the survival benefit of combination chemotherapy-radiation treatment may be limited to patients whose tumors contained specific deletions of genetic material in chromosomes 1 and 19 (1p/19q co-deletions).

"From this trial, it's clear that combining chemotherapy and radiation can significantly improve survival for certain patients," explained lead author Martin Van Den Bent, MD, Professor of Neuro-Oncology at Erasmus MC – Daniel den Hoed Cancer Center in Rotterdam, The Netherlands. "Not only do we now have a better treatment – we also have a genetic marker that can help us determine which patients will benefit, allowing us to personalize treatment for this challenging disease."

The 368 patients enrolled in this study had newly diagnosed, previously untreated anaplastic oligodendroglial tumors. They were randomly assigned to receive either radiation therapy alone or radiation followed by six cycles of chemotherapy with the drugs procarbazine, CCNU and vincristine, a regimen known as PCV. Currently, most patients with the disease are treated with either chemotherapy or radiation, but not both.

Progression-free survival was 24.3 months in the radiation/PCV group and 13.2 months in the radiation-only group. Overall survival was 42.3 months in the radiation/PCV group and 30.6 months in the radiation-only group.

When examined by genetic subtype, researchers found that the benefit of PCV and radiation was restricted to a subset of 80 patients known to have 1p/19q co-deletions. For these patients, treatment with radiation/PCV reduced their risk of dying by 44 percent, compared with patients who received radiation alone. Median overall survival was 9 years among patients with such deletions who received radiation alone, but this endpoint has not yet been reached in the radiation/PCV group after follow-up of almost 12 years. Among 236 patients without these co-deletions, overall survival was not statistically different between the treatment groups (25 months for the radiation/PCV group versus 22 months for radiation alone).

This study complements similar research also presented at the Annual Meeting and conducted by North American investigators. That Phase III study (Abstract #2008b) also found that giving both PCV and radiation therapy (with chemotherapy preceding radiation) improved survival for oligodendroglial tumor patients with 1p/19q co-deletions, compared with radiation alone, but not for patients without these deletions.

ASCO2012特集

小児がんに対する放射線治療は乳がんリスクを上昇させる（Abstract # CRA9513）

小児がんに対し放射線治療を受けた若年女性は、これまで考えられていたよりも低レベルの放射線照射でも乳がんリスクは上昇し得る

Lower levels of radiation than previously thought can increase risk of breast cancer among young women treated for childhood cancer

第48回 American Society of Clinical Oncology学会で発表されたスタディの結果、小児期がんに対し胸部への放射線照射を受けた小児がん既往女性は若年期に乳がんを発症するリスクが、BRCA1/2変異を有する女性と同等に高いことが示された。またこの結果から、これまで考えられていたよりもより多くの小児がん既往女性が影響を受けている可能性があることも示唆された。このスタディでは Childhood Cancer Survivor Study（CCSS）に参加した女性 1,200人余りおよび Women's Environmental Cancer and Radiation Epidemiology（WECARE）スタディに参加した女性の第一度近親者 4,570人のデータを解析した。WECAREは乳がんと診断され診断後1年以上生存している女性を組み入れた。総じて、小児がん既往者が50歳までに乳がんを発症する確率は24%であった。ホジキンリンパ腫既往者における乳がん発症率は30%であった。BRCA1変異を有する女性が50歳までに乳がんを発症する確率は31%であった。10～19Gyの低用量の放射線療法を受けた女性が 40歳までに乳がんを発症する率は 7%であり、20Gy以上の照射を受けた女性では12%であった。

Full Text

A study presented at the American Society of Clinical Oncology's 48th Annual Meeting finds that female survivors of childhood cancer treated with radiation to the chest had a high risk of developing breast cancer at a young age, comparable to that of BRCA1/2 mutation carriers. The findings also suggest that more survivors may be affected than previously thought.

Currently, screening guidelines for childhood cancer survivors recommend annual breast cancer screening for women who received moderate to high radiation doses of 20 Gray (Gy) or more to the chest as children, adolescents, or young adults. The researchers found that women treated with lower doses of chest radiation (10 to 19 Gy) also have an elevated risk of breast cancer at a young age, and may warrant screening as well.

"While radiation doses have decreased and techniques have improved, radiation is still an essential part of therapy for many childhood cancers," said Chaya S. Moskowitz, Ph.D., the study's lead author and an associate member and associate attending biostatistician at Memorial Sloan-Kettering Cancer Center, New York, NY. "The goal is to maximize the cure rates for childhood cancer while minimizing future health problems. For women treated with 20 Gy or more of chest radiation, the Children's Oncology Group recommends breast cancer surveillance with an annual mammogram and breast MRI, starting at age 25 or 8 years after the radiation (whichever is last). Our results suggest that young women treated with lower doses of radiation who are not currently being screened also have an elevated risk of breast cancer and might benefit from a similar screening strategy."

The study analyzed data from more than 1,200 women participating in the Childhood Cancer Survivor Study (CCSS) and 4,570 female first-degree relatives of participants in the Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study. WECARE enrolled women who had been diagnosed with breast cancer and survived at least one year after their diagnosis.

For the childhood cancer survivors overall, breast cancer incidence by age 50 was 24 percent. Among those who survived Hodgkin's lymphoma, the incidence was 30 percent. Among women who were carriers of a BRCA1 mutation, the incidence of breast cancer by age 50 was 31 percent.

The women treated with the lower doses of chest radiation ranging from 10 to 19 Gy had a breast cancer incidence of 7 percent by age 40 compared with 12 percent for those women treated with 20 Gy or higher. There are currently about 50,000 women in the U.S. who were treated with >20 Gy who should be receiving annual breast cancer screening, as recommended by Children's Oncology Group.

The authors estimate that there are another 7,000-9,000 women in the U.S who were treated with 10-19 Gy for childhood cancer and might benefit from annual screening as well.

To follow up on this study, Dr. Moskowitz has received a grant from the National Cancer Institute to build a model to predict the risk of breast cancer in childhood cancer survivors treated with chest radiation.

ASCO2012特集

化学療法誘発性末梢神経障害に有効な治療（Abstract # CRA9013）

デュロキセチンは有痛性化学療法誘発性末梢神経障害の第一の有効な治療法である

Duloxetine is first effective treatment for painful chemotherapy-induced peripheral neuropathy

第48回American Society of Clinical Oncology学会で発表された第3相スタディの結果、デュロキセチンは有痛性化学療法誘発性末梢神経障害の治療に有効であること—この発見によりがん診療が変わり、患者にとって重要な新たなQOLの解決法が得られる—が明らかにされた。デュロキセチンは現在米国において、うつ病および有痛性糖尿病性末梢神経障害に対し承認されている。今回のスタディでは、タキサンまたはプラチナ製剤治療による末梢神経障害に基づく高レベルの疼痛を訴えていた患者を、デュロキセチン投与後にプラセボを投与する群とプラセボ投与後にデュロキセチンを投与する群に無作為に割り付けた。参加者らは1日1錠の3mgカプセルを1週間内服した後に1日2カプセル（計60mg）をさらに4週間内服した。参加者らは疼痛に関するアンケートにスタディ開始時およびその後毎週回答した。疼痛が軽減したと回答したのはデュロキセチン内服中患者の59%であり、プラセボ内服群では39%であった。疼痛に変化がなかった割合は同等であった（デュロキセチン群30%対プラセボ群33%）。疼痛が増悪した割合はプラセボ群において高かった（デュロキセチン群11%対プラセボ群28%）。中等度から重度（グレード2以上）の倦怠感の発現率はデュロキセチン群においてプラセボ群よりも高かった（11%対3%）。

Full Text

A phase III study presented at the American Society of Clinical Oncology's 48th Annual Meeting found that duloxetine is effective in treating painful chemotherapy-induced peripheral neuropathy—a finding that will likely change oncology practice and offers an important new quality of life solution for patients. Duloxetine is currently approved in the United States for the treatment of depression and painful diabetic peripheral neuropathy.

Painful peripheral neuropathy affects 20 to 30 percent of cancer patients treated with taxanes and platinum-based chemotherapy and can be very debilitating. There has been no known effective treatment for peripheral neuropathy, which can lower the quality of life of patients during treatment and sometimes last for years afterwards.

"Duloxetine isn't perfect and didn't work for every patient in our study, but it was effective for a majority of people, and this was the first randomized clinical trial to show that any drug is effective for this terrible pain," said lead study author Ellen M. Lavoie Smith, Ph.D., an assistant professor in the School of Nursing at University of Michigan, Ann Arbor, MI. "We now have a treatment that could improve the quality of life for many of our patients."

In the study, 231 patients who had previously reported high levels of pain from peripheral neuropathy due to taxane or platinum treatment were randomized to duloxetine followed by placebo versus placebo followed by duloxetine.

"The participants took one 30mg capsule daily for one week, followed by two capsules daily (60mg total) for four additional weeks. The gradual dosing was important to reduce the side effects of duloxetine, which can include fatigue, dry mouth, sleepiness, and nausea," Dr. Smith said.

Patients completed a pain survey at the beginning of the study and then weekly. Results were as follows:

- Patients reporting decrease in pain: 59 percent for duloxetine, 39 percent for placebo.
- Patients reporting no change in pain: 30 percent for duloxetine, 33 percent for placebo.
- Patients reporting increase in pain: 11 percent for duloxetine, 28 percent for placebo.

The incidence of moderate to severe (grade 2 or greater) fatigue, the most commonly reported side effect, was higher in the duloxetine arm compared to placebo (11 percent vs. 3 percent).

ASCO2012特集

新たなPD-1標的免疫療法の有望な作用（Abstract # CRA2509）

治験段階の免疫療法薬は様々ながんの腫瘍縮小に有望であることが示された

Investigational immunotherapy agent shows promising tumor shrinkage in a range of cancers

第48回American Society of Clinical Oncologyで発表された第1相試験の結果、治験薬BMS-936558による治療により進行メラノーマ、腎および非小細胞肺がん（NSCLC）の腫瘍が最大4分の1に縮小したことが示された。この抗体薬は、がんに対する個体の免疫反応を阻害するPD-1と呼ばれるT細胞の重要なパスウェイを標的とする。このパスウェイを遮断することにより、BMS-936558は腫瘍細胞と戦う免疫系を再活性化させる可能性がある。研究者らは、標準治療を行ったにもかかわらず増悪したメラノーマ、大腸がん、NSCLC、前立腺がん、および腎がんの患者296人を組み入れた。奏効が認められたのはメラノーマ（26/94人；28%）、腎がん（9/33人；27%）、およびNSCLC（14/76；18%）であった。扁平上皮肺がんおよび非扁平上皮肺がんいずれにおいても奏効した。多くの患者において12か月以上にわたり奏効が認められ、この報告がなされている間もそれは持続していた。この薬剤の忍容性は全般的に良好であった；14%の患者に重篤な毒性が認められた。このトライアルのサブ解析の結果から、がん細胞上のバイオマーカー（PD-1と呼ばれる蛋白質）の可能性も示唆された。このバイオマーカーはBMS-936558が奏効する患者を予知するのに役立つ可能性がある。

Full Text

Results from an early-stage study presented at the American Society of Clinical Oncology's 48th Annual Meeting show that treatment with the investigational drug BMS-936558 caused tumor shrinkage in up to a quarter of patients with advanced melanoma, kidney and non-small cell lung (NSCLC) cancers. This antibody drug targets a key pathway in T-cells called PD-1, which inhibits the body's immune response to cancer. By blocking this pathway, BMS-936558 may re-activate the immune system to fight tumor cells.

"It's exciting to see this degree of anti-tumor activity from a single agent among patients with a range of cancers that had progressed despite standard therapies," said Suzanne Topalian, M.D., Professor of Surgery and Oncology at the Johns Hopkins University School of Medicine. "We were especially surprised to see activity in nearly 20 percent of patients with lung cancer, who are historically unresponsive to immune-based therapies. These findings mark what is probably the strongest anti-lung cancer activity observed to date with any immunotherapy."

This Phase I trial with expansion cohorts enrolled 296 patients with melanoma, colorectal, NSCLC, prostate and renal cancer that had progressed despite standard therapies. Responses were observed in patients with melanoma (26/94 patients; 28%), renal cancer (9/33 patients; 27%), and NSCLC (14/76 patients; 18%).

esponses were seen both in patients with squamous and non-squamous cell subtypes of lung cancer. Many patients responded for 12 months or longer and had ongoing responses at the time of this report.

The drug was generally well tolerated; serious toxicities were observed in 14 percent of patients. Side effects were generally consistent with those seen in other immune-focused therapies for cancer.

A sub-analysis of data from the trial also hints at a potential biomarker on cancer cells – a protein called PD-L1 – that could help predict which patients will respond to BMS-936558. Investigators analyzed tumor samples obtained from 42 patients prior to treatment initiation, for expression of the PD-L1 protein on the surface of tumor cells. After correlating the results with response data, they noted that over one-third of patients with PD-L1 positive tumors responded to the drug (9/25 patients; 36%), while none of the 17 PD-L1 negative patients had a response. Additional studies are planned to further assess the potential role of PD-L1 as a predictive marker of response to anti-PD-1 therapy.

ASCO2012特集