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Practice UPDATE

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ONCOLOGY

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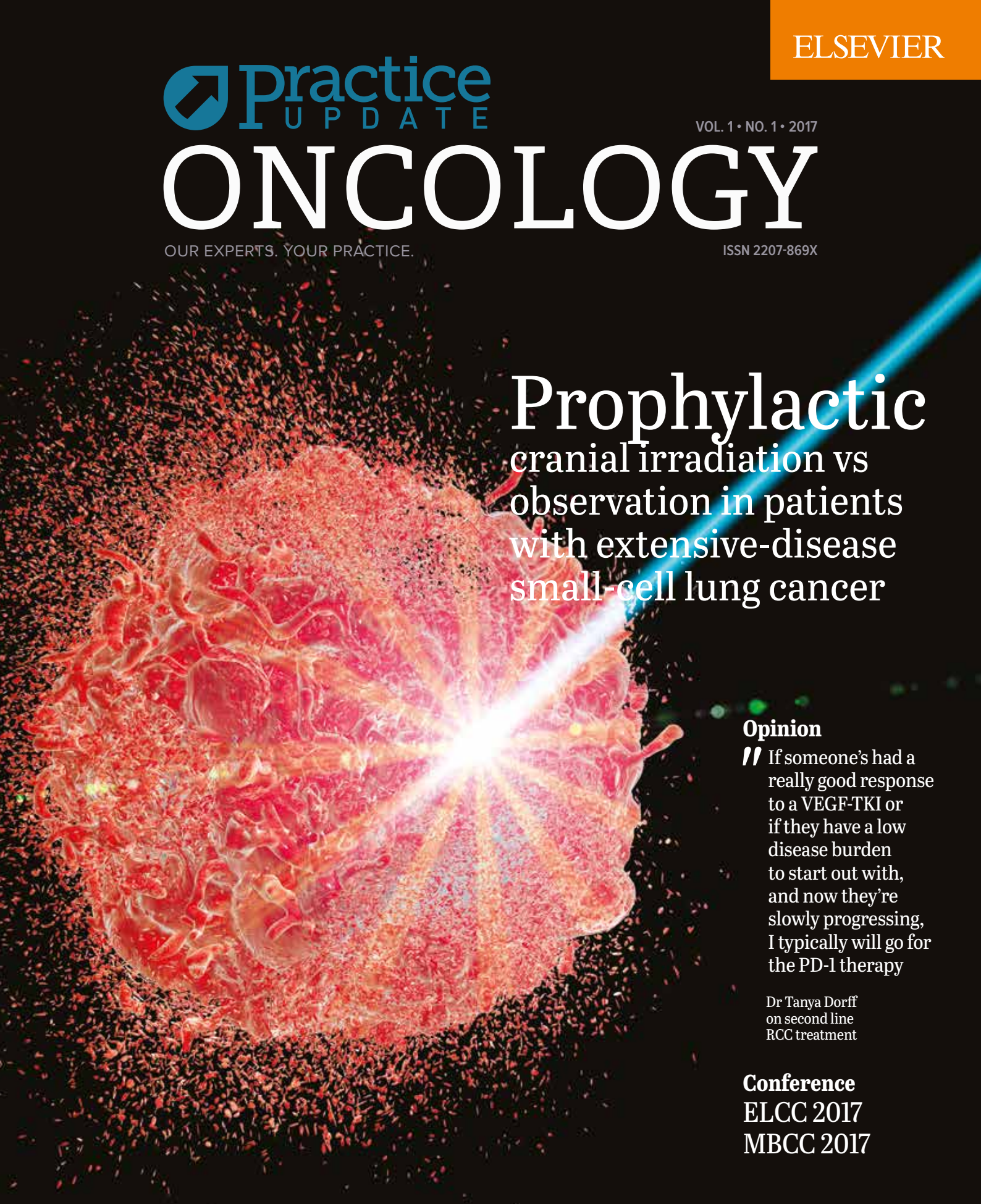


Prophylactic cranial irradiation vs observation in patients with extensive-disease small-cell lung cancer

Opinion

"If someone's had a really good response to a VEGF-TKI or if they have a low disease burden to start out with, and now they're slowly progressing, I typically will go for the PD-1 therapy

Dr Tanya Dorff on second line RCC treatment

Conference

ELCC 2017

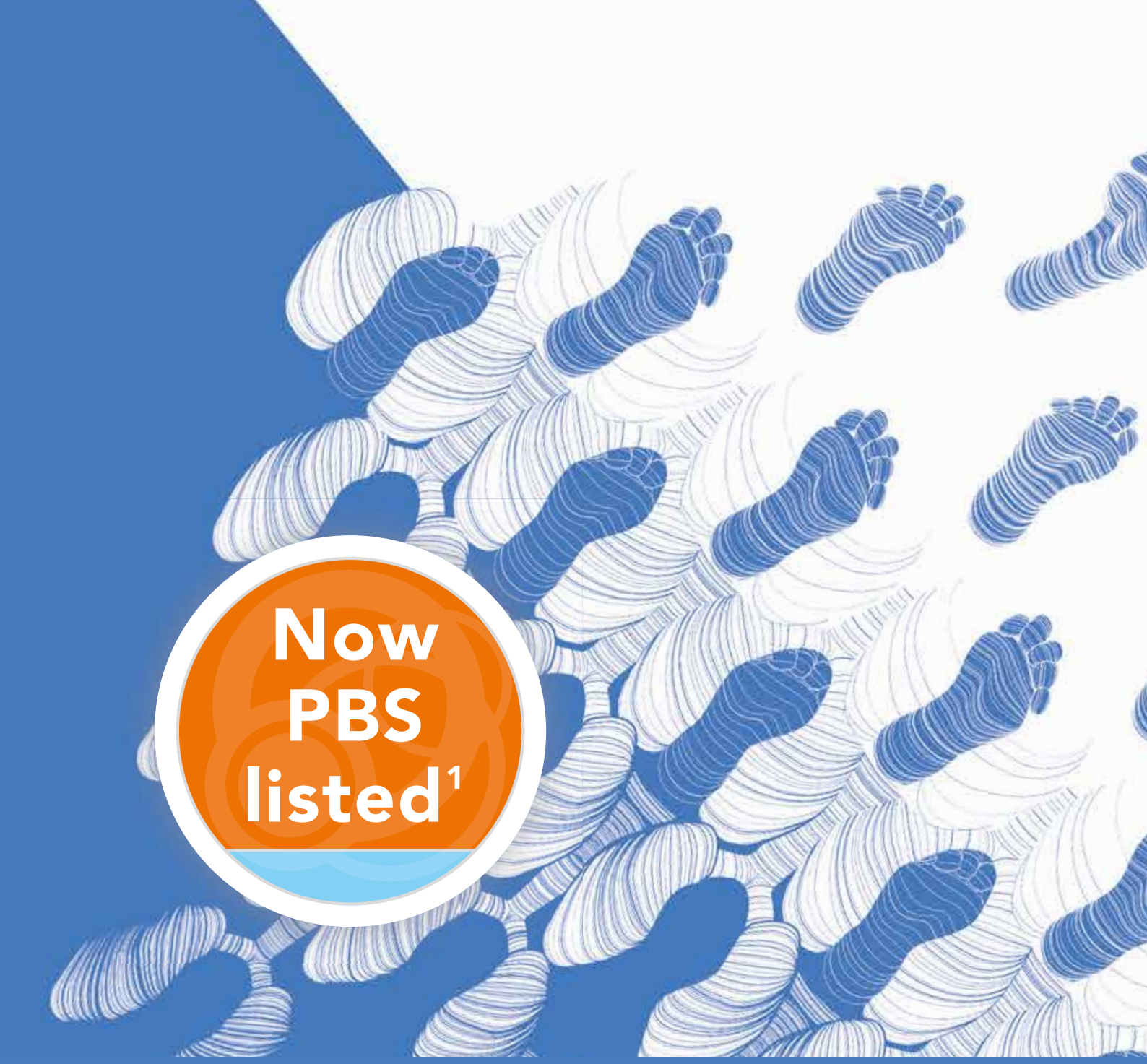
MBCC 2017

JOURNAL SCAN

Association between radiation therapy, surgery, or observation for localized prostate cancer and patient-reported outcomes after 3 years

Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone

Clinical calculator for early mortality in metastatic colorectal cancer: an analysis of patients from 28 clinical trials in the Aide et Recherche en Cancérologie Digestive Database



PBS Information: Authority Required. Refer to the PBS Schedule for full Authority information.

SERIOUS ADVERSE EVENTS

The following severe adverse events have been seen. Monitor closely and consider early dose reduction. See referenced () sections for details and appropriate management.

- QT interval prolongation (see Pharmacokinetics, Precautions, Adverse Effects, Dosage & Administration).
- Interstitial Lung Disease/Pneumonitis, including fatal cases (see Precautions, Adverse Effects, Dosage & Administration).
- Hepatotoxicity, including drug-induced liver injury (Pharmacokinetics, Precautions, Adverse Effects, Dosage & Administration).
- Gastrointestinal toxicity (Precautions, Adverse Effects, Dosage & Administration).

ZYKADIA has not been studied in patients with moderate and severe hepatic impairment.
ZYKADIA must be taken while fasting — any food consumption within a 2 hour period before or after administration increases systemic exposure up to 2-fold increasing the risk of toxicities, and also potentially exceeds the maximum dose tested, and the risks are unknown (see Pharmacokinetics, Dosage and Administration).

ZYKADIA should only be prescribed and supervised by a qualified physician experienced in the use of anticancer agents.

Please review Zykadia® (ceritinib) product information before prescribing.
Approved product information is available on request or online at
www.novartis.com.au/products/healthcare-professionals.shtml

NOVARTIS

ZYKADIA®
ceritinib

A PATH FORWARD FOR 2L ALK+ NSCLC[2]

ZYKADIA® (ceritinib) is indicated as monotherapy for the treatment of adult patients with ALK+ locally advanced or metastatic NSCLC whose disease has progressed on or who are intolerant of crizotinib.[2]

Note to indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established.[2]

Indication: ZYKADIA is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on or who are intolerant of crizotinib. Note to Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Precautions:** Hepatotoxicity; Interstitial lung disease / Pneumonitis, QT interval prolongation Bradycardia, Gastrointestinal toxicity, Hyperglycemia, Pancreatic toxicity, Women of child-bearing potential, Pregnancy, Lactation. Fertility, Children (below 18 years) See full PI. **Interactions:** Strong inhibitors or inducers of CYP3A and P-gp. Gastric acid-reducing agents (proton pump inhibitors, H2-receptor antagonists, antacids) Avoid co-administration CYP3A & CYP2C9 substrates known to have narrow therapeutic indices Exercise caution with concomitant use of CYP2A6 and CYP2E1 substrates and carefully monitor adverse drug reactions. Risk for induction of other PXR regulated enzymes apart from CYP3A4 cannot be completely excluded. Effectiveness of concomitant administration of oral contraceptives may be reduced. ZYKADIA capsules must be taken on an empty stomach. No food should be eaten for at least two hours before and two hours after the dose of ZYKADIA is taken. Patients should be instructed to avoid grapefruit or grapefruit juice as they may inhibit CYP3A in the gut wall and increase the bioavailability of ZYKADIA. See full PI. **Dosage and administration:** Recommended dose is 750 mg taken orally once daily at the same time each day. Maximum recommended dose is 750 mg daily. ZYKADIA capsules must be taken on an empty stomach. No food should be eaten for at least two hours before and two hours after the dose of ZYKADIA is taken. The dose should be reduced by decrements of 150 mg daily. ZYKADIA should be discontinued in patients unable to tolerate 300 mg daily. See full PI for dose interruption, reduction, or discontinuation of ZYKADIA in the management of select adverse drug reactions. Use caution in patients with severe renal impairment. See full PI. **Side effects: Very common (≥10%):** Anemia, decreased appetite, diarrhea, nausea, vomiting, abdominal pain, constipation, esophageal disorder, rash, fatigue, liver laboratory test abnormalities and blood creatinine increased. **Common (1 to 10%):** Hyperglycemia, hypophosphatemia, vision disorder, pericarditis, bradycardia, pneumonitis, abnormal liver function tests, renal failure, renal impairment, electrocardiogram QT prolonged, lipase increased, and amylase increased. **Uncommon (0.1 to 1%):** Hepatotoxicity and pancreatitis. See full PI (*ldk010816i*).

2L: second line, **ALK+:** anaplastic lymphoma kinase positive, **NSCLC:** non-small cell lung cancer

References: 1. Pharmaceutical Benefits Scheme (PBS) www.pbs.gov.au **2.** ZYKADIA Product Information

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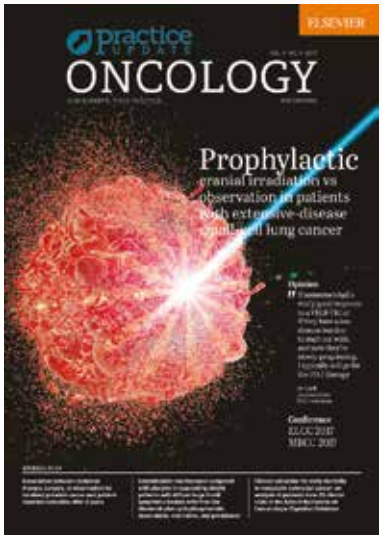

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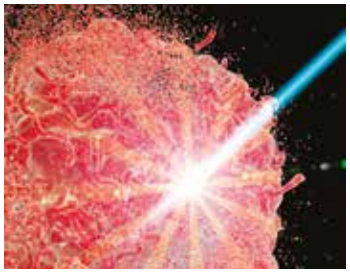


Conference

Features

RESEARCH

Editor's picks

Lymphomas

Head & Neck

Prostate

Colon & Rectum

Prophylactic cranial irradiation vs observation in patients with extensive-disease small-cell lung cancer

The Lancet Oncology

Take-home message

- The authors of this randomized, open-label, phase III study assessed the efficacy of prophylactic cranial irradiation vs observation in the treatment of extensive-disease small cell lung cancer. During a planned interim analysis, the Bayesian predictive probability of prophylactic cranial irradiation being superior to observation was 0.011%, resulting in early study termination.
- Prophylactic cranial irradiation did not result in longer overall survival compared with observation in patients with extensive-disease small cell lung cancer.

Abstract

BACKGROUND Results from a previous phase 3 study suggested that prophylactic cranial irradiation reduces the incidence of symptomatic brain metastases and prolongs overall survival compared with no prophylactic cranial irradiation in patients with extensive-disease small-cell lung cancer. However, because of the absence of brain imaging before enrollment and variations in chemotherapeutic regimens and irradiation doses, concerns have been raised about these findings. We did a phase 3 trial to reassess the efficacy of prophylactic cranial irradiation in the treatment of extensive-disease small-cell lung cancer.

METHODS We did this randomised, open-label, phase 3 study at 47 institutions in Japan. Patients with extensive-disease small-cell lung cancer who had any response to platinum-based doublet chemotherapy and no brain metastases on MRI were randomly assigned (1:1) to receive prophylactic cranial irradiation (25 Gy in ten daily fractions of 2.5 Gy) or observation. All patients were required to have brain MRI at 3-month intervals up to 12 months and at 18 and 24 months after enrolment. Randomisation was done by computer-generated allocation sequence, with age as a stratification factor and minimisation by institution, Eastern Cooperative Oncology Group performance status, and response to initial chemotherapy. The primary endpoint was overall survival, analysed in the intention-to-treat population.

FINDINGS Between April 3, 2009, and July 17, 2013, 224 patients were enrolled and randomly assigned (113 to prophylactic cranial irradiation and 111 to observation). In the planned interim analysis on June 18, 2013, of the first 163 enrolled patients, Bayesian predictive probability of prophylactic cranial irradiation being superior to observation was 0.011%, resulting in early termination of the study because of futility. In the final analysis, median overall survival was 11.6 months (95% CI 9.5–13.3) in the prophylactic cranial irradiation group and 13.7 months (10.2–16.4) in the observation group (hazard ratio 1.27, 95% CI 0.96–1.68; p=0.094). The most frequent grade 3 or worse adverse events at 3 months were anorexia (six [6%] of 106 in the prophylactic cranial irradiation group vs two [2%] of 111 in the observation group), malaise (three [3%] vs one [<1%]), and muscle weakness in a lower limb (one [<1%] vs six [5%]). No treatment-related deaths occurred in either group.

INTERPRETATION In this Japanese trial, prophylactic cranial irradiation did not result in longer overall survival compared with observation in patients with extensive-disease small-cell lung cancer. Prophylactic cranial irradiation is therefore not essential for patients with extensive-disease small-cell lung cancer with any response to initial chemotherapy and a confirmed absence of brain metastases when patients receive periodic MRI examination during follow-up.

Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2017 Mar 23;[EPub Ahead of Print], T Takahashi, T Yamanaka, T Seto, et al.

COMMENT

By Minesh P Mehta MD, FASTRO

This is a significant trial as it contradicts the findings of the only other prior major randomized trial in extensive-stage small cell lung cancer patients, the EORTC trial, which showed a survival benefit from PCI.[1] The Japanese trial failed to corroborate this finding. So, why the discordance? The results of one or the other trial were a fluke. The dose regimens were different (25 Gy in 10 fractions for the Japanese trial, and mostly 20 Gy in 5 fractions for the EORTC trial); however, when corrected for radiobiological equivalence, these are actually quite comparable regimens. The Japanese trial allowed patients with ANY response to chemotherapy to be enrolled, similar to the EORTC trial; the implication here is that it is quite possible that there was a discordance in terms of the number of patients with complete response (CR) or near-CR versus those with lesser response to systemic therapy (relative to extracranial disease) between the trials. Data for limited-stage SCLC show categorical survival benefit from PCI, especially for patients with CR or near-CR. It is therefore possible that it is the subset of patients with extensive-stage SCLC with CR or near-CR who are the ones who actually derive a survival benefit from PCI. Perhaps the next step is a meta-analysis of these two trials, focusing on this question.

Reference

1. Slotman B, Faivre-Finn C, Kramer G, et al. *N Engl J Med* 2007; 357(7): 664-672.

Dr Mehta is Deputy Director of the Miami Cancer Institute and Chief of Radiation Oncology. He is also the NRG/Oncology Brain Tumor Committee Chair.

Nivolumab in advanced hepatocellular carcinoma (CheckMate 040)

The Lancet

Take-home message

- This phase I/II multisite, open-label dose-expansion and escalation trial assessed the safety and efficacy of the PD-1 inhibitor nivolumab in patients with advanced hepatocellular carcinoma, with or without chronic viral hepatitis. The primary endpoints were objective response rate and safety and tolerability for the dose-escalation phase. Among the 48 patients in the dose-escalation phase of the study, treatment with intravenous nivolumab at 0.1 to 10 mg/kg every 2 weeks was tolerable, with a manageable safety profile. Treatment was discontinued in 96% of patients, 88% of whom due to disease progression. The maximum tolerated dose was not reached. Grade 3/4 treatment-related adverse events occurred in 25% of patients. Of the 214 patients in the expansion phase treated with nivolumab 3 mg/kg every 2 weeks, 63% died from non-treatment related events. In the dose-escalation and expansion phases, the objective response rates were 15% and 20%, respectively.
- In patients with advanced hepatocellular carcinoma, nivolumab had a manageable safety profile and a durable objective response, indicating the drug's potential in this population.

Abstract

BACKGROUND For patients with advanced hepatocellular carcinoma, sorafenib is the only approved drug worldwide, and outcomes remain poor. We aimed to assess the safety and efficacy of nivolumab, a programmed cell death protein-1 (PD-1) immune checkpoint inhibitor, in patients with advanced hepatocellular carcinoma with or without chronic viral hepatitis.

METHODS We did a phase 1/2, open-label, non-comparative, dose escalation and expansion trial (CheckMate 040) of nivolumab in adults (≥18 years) with histologically confirmed advanced hepatocellular carcinoma with or without hepatitis C or B (HCV or HBV) infection. Previous sorafenib treatment was allowed. A dose-escalation phase was conducted at seven hospitals or academic centres in four countries or territories (USA, Spain, Hong Kong, and Singapore) and a dose-expansion phase was conducted at an additional 39 sites in 11 countries (Canada, UK, Germany, Italy, Japan, South Korea, Taiwan). At screening, eligible patients had Child-Pugh scores of 7 or less (Child-Pugh A or B7) for the dose-escalation phase and 6 or less (Child-Pugh A) for the dose-expansion phase, and an Eastern Cooperative Oncology Group performance status of 1 or less. Patients with HBV infection had to be receiving effective antiviral therapy (viral load <100 IU/mL); antiviral therapy was not required for patients with HCV infection. We excluded patients previously treated with an agent targeting T-cell costimulation or checkpoint pathways. Patients received intravenous nivolumab 0.1–10 mg/kg every 2 weeks in the dose-escalation phase (3+3 design). Nivolumab 3 mg/kg was given every 2 weeks in the dose-expansion phase to patients in four cohorts: sorafenib untreated or intolerant without viral hepatitis, sorafenib progressor without viral hepatitis, HCV infected, and HBV infected. Primary endpoints were safety and tolerability for the escalation phase and objective response rate (Response Evaluation Criteria In Solid Tumors version 1.1) for the expansion phase. This study is registered with ClinicalTrials.gov, number NCT01658878.

FINDINGS Between Nov 26, 2012, and Aug 8, 2016, 262 eligible patients were treated (48 patients in the dose-escalation phase and 214 in the dose-expansion phase). 202 (77%) of 262 patients have completed treatment and follow-up is ongoing. During dose escalation, nivolumab showed a manageable safety profile, including acceptable tolerability. In this phase, 46 (96%) of 48 patients discontinued treatment, 42 (88%) due to disease progression. Incidence of treatment-related adverse events did not seem to be associated with dose and no maximum tolerated dose was reached. 12 (25%) of 48 patients had grade 3/4 treatment-related adverse events. Three (6%) patients had treatment-related serious adverse events (pemphigoid, adrenal insufficiency, liver disorder). 30 (63%) of 48 patients in the dose-escalation phase died (not determined to be related to nivolumab therapy). Nivolumab 3 mg/kg was chosen for dose expansion. The objective response rate was 20% (95% CI 15–26) in patients treated with nivolumab 3 mg/kg in the dose-expansion phase and 15% (95% CI 6–28) in the dose-escalation phase.

INTERPRETATION Nivolumab had a manageable safety profile and no new signals were observed in patients with advanced hepatocellular carcinoma. Durable objective responses show the potential of nivolumab for treatment of advanced hepatocellular carcinoma.

Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017 Apr 20;[EPub Ahead of Print], AB El-Khoueiry, B Sangro, T Yau, et al.

> "It is conceivable that PD-1 antibodies will soon become one of the standards of care in the management of advanced HCC, likely making inroads into first-line therapy.

COMMENT

By Axel Grothey MD

Advanced hepatocellular carcinoma (HCC) is a malignancy with a high unmet need. In spite of recent advances in the medical therapy of this disease with the expected approval of regorafenib as second-line therapy after prior sorafenib treatment, outcomes overall are still poor.

The common viral etiology of HCC had long raised the hope that immune therapies could be effective. The current study now presents clear proof of activity of a PD-1 antibody in HCC. As with other GI malignancies wherein PD-1 antibodies have been shown to be active, the actual response rate is only in the range of about 20%, but some of these responses are strikingly durable. In addition, a substantial number of patients experienced prolonged stable disease. Interestingly, the activity of the antibody appeared to be independent of an underlying viral etiology.

It is conceivable that PD-1 antibodies will soon become one of the standards of care in the management of advanced HCC, likely making inroads into first-line therapy. As in other cancers, one of the challenges for the future will be to turn the nonresponders to immunotherapy into responders with further manipulations and activation of the immune system.

Dr Grothey is a consultant in the Division of Medical Oncology, Department of Oncology, at Mayo Clinic.

Localized prostate cancer treatment and patient-reported outcomes after 3 years

JAMA: The Journal of the American Medical Association

Take-home message

- The authors evaluated various treatment modalities within the context of localized prostate cancer and their influence on patient outcomes. Within a cohort of 2550 men, 59.7% underwent radical prostatectomy, 23.5% underwent external beam radiotherapy (EBRT), and 16.8% underwent active surveillance. After 3 years, patients who underwent radical prostatectomy experienced a greater decrease in sexual function and worse urinary incontinence than those who underwent EBRT or active surveillance. Notably, radical prostatectomy was also associated with fewer urinary irritative symptoms than active surveillance.
- The authors conclude that comparing adverse events associated with various treatments for localized prostate cancer can improve patient counseling and suitability of therapy choice.

> "...comparing adverse events associated with various treatments for localized prostate cancer can improve patient counseling and suitability of therapy choice.

Abstract

IMPORTANCE Understanding the adverse effects of contemporary approaches to localized prostate cancer treatment could inform shared decision making.

OBJECTIVE To compare functional outcomes and adverse effects associated with radical prostatectomy, external beam radiation therapy (EBRT), and active surveillance.

DESIGN, SETTING, AND PARTICIPANTS Prospective, population-based, cohort study involving 2550 men (≤80 years) diagnosed in 2011–2012 with clinical stage cT1-2, localized prostate cancer, with prostate-specific antigen levels less than 50 ng/mL, and enrolled within 6 months of diagnosis.

EXPOSURES Treatment with radical prostatectomy, EBRT, or active surveillance was ascertained within 1 year of diagnosis.

MAIN OUTCOMES AND MEASURES Patient-reported function on the 26-item Expanded Prostate Cancer Index Composite (EPIC) 36 months after enrollment. Higher domain scores (range, 0–100) indicate better function. Minimum clinically important difference was defined as 10 to 12 points for sexual function, 6 for urinary incontinence, 5 for urinary irritative symptoms, 5 for bowel function, and 4 for hormonal function.

RESULTS The cohort included 2550 men (mean age, 63.8 years; 74% white, 55% had intermediate- or high-risk disease), of whom 1523 (59.7%) underwent radical prostatectomy, 598 (23.5%) EBRT, and 429 (16.8%) active surveillance. Men in the EBRT group were older (mean age, 68.1 years vs 61.5 years, P<0.001) and had worse baseline sexual function (mean score, 52.3 vs 65.2, P<0.001) than men in the radical prostatectomy group. At 3 years, the adjusted mean sexual domain score for radical prostatectomy decreased more than for EBRT (mean difference, -11.9 points; 95% CI, -15.1 to -8.7). The decline in sexual domain scores between EBRT and active surveillance was not clinically significant (-4.3 points; 95% CI, -9.2 to 0.7). Radical prostatectomy was associated with worse urinary incontinence than EBRT (-18.0 points;

COMMENT

By Thomas J Guzzo MD, MPH

There are two studies that go hand-in-hand; one is from the University of North Carolina[1] and the other is from Vanderbilt University.[2] Both of these studies essentially used databases and registry data to try to ascertain quality of life after treatment for prostate cancer of men undergoing various types of local therapy. The first study out of UNC involved external beam radiation therapy, brachytherapy, active surveillance, and radical prostatectomy. The Vanderbilt study involved external beam radiation therapy, radical prostatectomy, and active surveillance; the two studies found slightly different results.

The UNC study looked at validated quality-of-life questionnaires for the different treatments, and, as you would expect, found detriments in quality of life associated with radical prostatectomy and radiation relative to active surveillance early on. But, interestingly enough, by 24 months the main scores for active treatment versus active surveillance were not that significantly different.

So, at least based on the results of this study cohort, you could say that men who get upfront treatment for their prostate cancer are going to have decreased quality of life or functional scores for a period of time upwards to 24 months, at which point they reach a threshold on par with that of their active surveillance counterparts. I think that may be helpful for patients when they are considering treatment for prostate cancer in the context of what they're willing to undergo and at what risk.

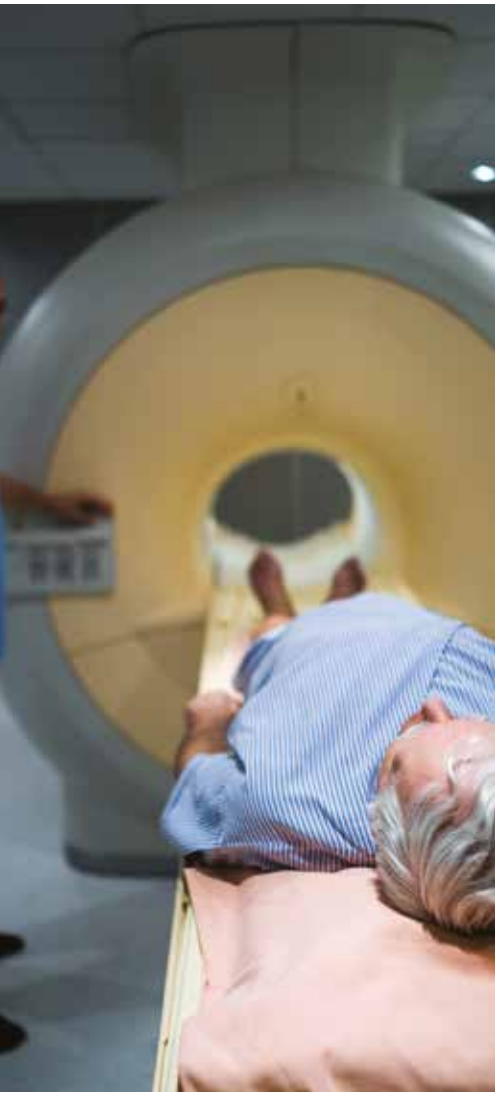
The Vanderbilt article, again very similar, looked at validated questionnaires for men who underwent prostate cancer treatment. The authors found slightly different results. That's the problem with a lot of these studies – the results don't all correspond; but again, as you would expect, the patients who were treated had decreased quality-of-life scores over the short term.

I think these two studies are interesting. I think we are going to see more and more of these types of studies, and the reason why is because a decision about treatment represents extremely complex decision-making for the patient and the physician. A lot of what ultimately drives the decision is what the patient is willing to accept from a side-effect profile standpoint, and studies like these, when presented to patients, can help them make some of these decisions because they provide tangible quantitative data as to what might happen to someone if he chose this treatment relative to a different treatment at least over a short period of time – 3 months, 12 months, 24 months.

References

1. Chen RC, Basak R, Meyer AM, et al. *JAMA* 2017;317(11):1141-1150.
2. Barocas DA, Alvarez J, Resnick MJ, et al. *JAMA* 2017;317(11):1126-1140.

Dr Guzzo is Chief of Urology and Associate Program Director at the University of Pennsylvania.



95% CI, -20.5 to -15.4) and active surveillance (-12.7 points; 95% CI, -16.0 to -9.3) but was associated with better urinary irritative symptoms than active surveillance (5.2 points; 95% CI, 3.2 to 7.2). No clinically significant differences for bowel or hormone function were noted beyond 12 months. No differences in health-related quality of life or disease-specific survival (3 deaths) were noted (99.7–100%).

CONCLUSIONS AND RELEVANCE In this cohort of men with localized prostate cancer, radical prostatectomy was associated with a greater decrease in sexual function and urinary incontinence than either EBRT or active surveillance after 3 years and was associated with fewer urinary irritative symptoms than active surveillance; however, no meaningful differences existed in either bowel or hormonal function beyond 12 months or in in other domains of health-related quality-of-life measures. These findings may facilitate counseling regarding the comparative harms of contemporary treatments for prostate cancer.

Association between radiation therapy, surgery, or observation for localized prostate cancer and patient-reported outcomes after 3 years *JAMA* 2017 Mar 21;317(11)1126-1140, DA Barocas, J Alvarez, MJ Resnick, et al.

Outcomes of HER2-positive patients with newly diagnosed stage IV or recurrent breast cancer undergoing first-line trastuzumab-based therapy

Clinical Breast Cancer

Take-home message

- This multicenter cohort study evaluated clinical outcomes in patients with de novo (n = 113) or recurrent (n = 303) HER2-positive metastatic breast cancer undergoing first-line trastuzumab-based therapy. Compared with patients in the recurrence cohort, those in the de novo cohort had worse baseline characteristics, received more aggressive first-line treatment, and had better survival. Patients in the de novo cohort who underwent surgery of the primary tumor experienced improved progression-free survival (aHR, 0.44; P = 0.001) and overall survival (aHR, 0.49; P = 0.029) relative to those who did not.
- Among patients taking first-line trastuzumab, those with de novo HER2-positive disease experienced significantly better survival outcomes than those with recurrent disease, particularly those patients who had surgery of the primary tumor.

Abstract

BACKGROUND To compare the patterns of care and clinical outcomes of HER2-positive metastatic breast cancer (MBC) patients with de novo or recurrent disease undergoing first-line trastuzumab-based therapy.

METHODS This is a multicenter retrospective cohort study including consecutive patients with HER2-positive MBC receiving first-line trastuzumab-based therapy. Analyses on treatment response and effectiveness were conducted according to type of metastatic presentation (i.e. de novo vs. recurrent disease). Exploratory analyses evaluated whether the use of surgery of the primary tumor in the de novo cohort influenced patients' survival.

RESULTS From January 2000 to December 2013, 416 patients were included in the study, 113 (27.2%) presented with de novo MBC and 303 (72.8%) with recurrent disease. As compared to patients in the recurrence cohort, those in the de novo cohort had worse baseline characteristics, received more aggressive first-line treatments and showed better survival, with an adjusted hazard ratio (HR) for progression-free survival (PFS) of 0.65 (95% confidence intervals [CI], 0.43–0.97; p = 0.035) and for overall survival (OS) of 0.53 (95% CI, 0.30–0.95; p = 0.034). In the de novo cohort, the 54 (47.8%) patients who underwent surgery of the primary tumor had significantly better PFS (adjusted HR, 0.44; 95% CI, 0.26–0.72; p = 0.001) and OS (adjusted HR, 0.49; 95% CI, 0.26-0.93; p = 0.029) than those who did not undergo surgery.

CONCLUSION Patients with de novo HER2-positive MBC showed significantly better survival outcomes than those with recurrent disease. In this population, surgery of the primary breast tumor was associated with better outcomes.

Patterns of care and clinical outcomes of HER2-positive metastatic breast cancer patients with newly diagnosed stage IV or recurrent disease undergoing first-line trastuzumab-based therapy: a multicenter retrospective cohort study. *Clin Breast Cancer* 2017 Apr 10;[EPub Ahead of Print], M Lambertini, AR Ferreira, A Di Meglio, et al.

COMMENT

By Lillie D Shockney RN, BS, MAS

The wide period (2000–2013) that this study encompassed includes the time when patients with distant recurrence did not necessarily have these lesions biopsied to reevaluate their ER, PR, and HER2 receptors. So, it would therefore seem possible that patients who were originally HER2-positive, and whose distant recurrence wasn't biopsied, may have become HER2-negative. If this is a possibility, then it would cloud the results of this study.

Ms Shockney is University Distinguished Service Professor of Breast Cancer, and Administrative Director at Johns Hopkins Breast Center and Cancer Survivorship Programs.

European Lung Cancer Conference 2017

5–8 MAY 2017 • GENEVA, SWITZERLAND

Exciting developments in lung cancer, particularly in immunotherapy, took centre stage at the European Lung Cancer Conference 2017. Among these were important new data on the activity of anti-PD-L1 antibodies in the first-line treatment of squamous NSCLC. The PracticeUpdate Editorial Team reports.

Patients with NSCLC respond best to salvage chemotherapy when pretreated with PD-1/PD-L1 inhibitors

Patients with advanced non-small-cell lung cancer who require salvage chemotherapy are 30% more likely to achieve a partial response when pretreated with a programmed death-1(PD-1)/PD-ligand 1 (L1) checkpoint inhibitor than those not pretreated with the medication, report preliminary findings of a retrospective analysis.

Sacha Rothschild, MD, PhD, of University Hospital Basel, Switzerland, said that these preliminary findings could potentially open the door to a new way of sequencing cancer therapy.

He said, "Our results are of utmost importance for patients with non-small-cell lung cancer. Checkpoint inhibitors are the standard of care for patients with non-small-cell lung cancer in the second-line setting after chemotherapy and are used for a subset of patients with high PD-L1 expression as front-line therapy."

He continued, "It is still unclear how to treat patients who do not respond to immune checkpoint inhibitors or who progress after initially responding to these agents. The activity of conventional chemotherapy in this setting has not yet been investigated. These results are good news for patients who progress after immunotherapy and are still fit enough to receive further palliative therapy."

Eighty-two patients with stage 4 non-small-cell

White blood cell count predicts response to immunotherapy for lung cancer

White blood cell counts can predict whether or not patients with lung cancer will benefit from immunotherapy, reports an assessment of the ability of white blood cell counts to predict whether lung cancer patients responded to nivolumab.

Marcello Tiseo, MD, of the University Hospital of Parma, Italy, explained, "Immune checkpoint inhibitors such as nivolumab and pembrolizumab improve overall survival significantly in some, but not all, patients with non-small-cell lung cancer. Researchers are seeking predictive biomarkers to select patients who will benefit from this treatment to avoid unnecessary toxicity and a waste of resources in patients who will not respond."

He continued, "Programmed death – ligand 1 (PD-L1) expression in a biopsy of tumor tissue is used to select patients but is not completely accurate, possibly because the biopsy sample does not reflect the evolving immune response. Biomarkers in the blood are easier to obtain and may be better indicators of immune response."

The study included 54 patients with non-small-cell lung cancer who received nivolumab at a dose of 3 mg per kilogram of body weight every 14 days. White blood cells were counted at baseline, after two nivolumab cycles, and after four nivolumab cycles. Researchers compared white blood cell counts between responders and nonresponders to nivolumab.

White blood cell counts at baseline and during therapy predicted whether patients would respond to nivolumab treatment. A greater number and concentration of natural killer cells at baseline was associated with response to nivolumab, as was an increase in the number of natural killer cells during treatment. Responders to nivolumab also harbored a greater number and concentration of CD8-positive T cells that expressed PD-1.

Dr Tiseo said, "The number and function of natural killer cells and frequency of PD-1 expression in CD8-positive T cells could be predictive biomarkers for nivolumab treatment in advanced non-small-cell lung cancer. Identification of a panel of blood predictive biomarkers would enable early identification of patients most likely to benefit from anti-PD-1 and anti-PD-L1 treatment."

Stefan Zimmermann, MD, of the Hôpital Cantonal, Fribourg, Switzerland, concluded, "In the era of precision medicine and increasing healthcare costs we urgently need predictive biomarkers to select patients who will benefit from a specific therapy."

He continued, "This study found that baseline levels of certain white blood cells play a role in predicting response to immunotherapy in patients with lung cancer. These new factors should be investigated in future clinical trials, together with tumor PD-L1 expression and other markers that constitute the cancer immunogram to predict whether or not patients will benefit from treatment."

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lung cancer, including adenocarcinoma (n=63), squamous cell carcinoma (n=18), and one case of large cell carcinoma were analyzed.

Sixty-seven patients had been treated previously with a PD-1/PD-L1 inhibitor, including 56 patients who received nivolumab; seven, pembrolizumab; and four, atezolizumab.

The remaining 15 patients, who had not been treated with PD-1/PD-L1 inhibitors, served as controls. All patients had been pretreated with chemotherapy, with a mean of 2.37 prior regimens among cases and 1.93 in controls. Salvage chemotherapy included docetaxel (62%), pemetrexed (20%), paclitaxel (6%), and others (12%).

Computed tomography scans performed within the first month and then every 6 weeks showed a significantly higher partial response rate in cases than in controls (27% vs 7%, odds ratio 0.3, $P < 0.0001$).

Stable disease was seen in 51% of cases and 53% of controls, and progressive disease in 22% of cases vs 40% of controls.

Multiple logistic regression showed that age, gender, number of prior chemotherapy regimens, tumor histology, smoking status, and different salvage chemotherapy regimens were not independently associated with the likelihood of achieving partial response.

Dr Rothschild said, "At this point we can only speculate on reasons for the better response in patients pretreated with checkpoint inhibitors. Probably, activation of the immune system by checkpoint inhibition might render tumor cells more sensitive to chemotherapy. Or chemotherapy may help tumor-specific T-cells to enter the tumor microenvironment and exert their function."

Dr Rothschild said that investigations are ongoing into the duration of response and toxicity, and he cautioned that this finding must be explored further in larger and prospective cohorts.

Marina Garassino, MD, of the National Cancer Institute of Milan (Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori) was enthusiastic about the potential implications.

She said, "This was the first research to suggest that chemotherapy could potentially work better after immunotherapy. All of us treating patients with immunotherapy have had a feeling about this possibility because we've seen unexpected results with some patients."

She continued, "This was the first study to describe this phenomenon formally. Though the results were very preliminary, they suggested that immunotherapy can change the natural history of the disease and the tumor microenvironment, therefore rendering the tumor more sensitive to chemotherapy. This could potentially point to new areas of research and new sequences of treatment."

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Annual influenza vaccine may pose greater risk in patients with lung cancer receiving immunotherapy

Lung cancer patients treated with programmed death 1 (PD-1)/PD-ligand 1 (L1) checkpoint inhibitors may be at increased risk of adverse events after receiving the seasonal influenza vaccination, results of the first study to measure this effect show.

Sacha Rothschild, MD, PhD, of University Hospital Basel, Switzerland, said the results offer the first hint of a possible contraindication to two routine treatments in this population.

"Use of immune checkpoint inhibitors is now standard clinical practice for many oncology patients," he said, "and these patients, particularly those with lung cancer, also face increased risk for complications from influenza."

He continued, "Though routine influenza vaccination has long been recommended for cancer patients, it might trigger an exaggerated immune response in this subgroup receiving checkpoint inhibitors." He cautioned that these preliminary results must be tested in a larger study.

The prospective study included 23 patients (mean age 58.7 years), mostly with non-small-cell lung cancer (n = 16), but also with renal cell carcinoma (n=4), and melanoma (n=3).

A little over half of patients had received at least two lines of chemotherapy and all were receiving the PD-1/PD-L1 inhibitor nivolumab, except one who was receiving pembrolizumab.

Patients were vaccinated with a trivalent influenza vaccination in 2015 and followed for safety, efficacy, and frequency of immune-related adverse events. A control group of 10 age-matched, healthy partners of the patients received the same vaccine.

All patients showed adequate immune response to the vaccine, developing antibody titers against all three viral strains. No severe adverse events attributable to the vaccine were noted in the first 30 days after vaccination.

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The rate of local irritation (all grade 1) at the injection site (the deltoid muscle) was similar in patients and controls. No influenza infection was diagnosed in any vaccinated patients during the 2015/2016 influenza season.

An unusually high frequency of immune-related adverse events (52.2%) was observed, however, with six patients (26.1%) experiencing severe grade 3 or 4 immune-related adverse events.

Dr Rothschild said, "This frequency was significantly higher than the rate of immune-related adverse events in unvaccinated patients treated with PD-1/PD-L1 inhibitors." He added that the expected rate is about 25.5% at his center (9.8% for grade 3 or 4 events) and a rate of 30–35% is reported in the literature. "Our hypothesis is that the vaccine results in overwhelming activation of the immune system in this population."

The most common immune-related adverse events reported were skin rashes and arthritis (13% each), followed by colitis and encephalitis (8.7% each), hypothyroidism, pneumonitis, and neuropathy (4.3% each).

PD-1 blockade may increase the immune response and induce an inflammatory syndrome, so the researchers measured inflammatory chemokines in patients' peripheral blood to assess potential induction of a subclinical inflammatory syndrome.

No significant change in inflammatory chemokine levels was observed in either patients or controls during the early phase after vaccination.

Dr Rothschild said, "Though the observed rate of immune-related adverse events in our cohort was alarming, we believe the severe complications of influenza infection, including pneumonia and respiratory failure, are a concern in patients with lung cancer receiving immunotherapy because these patients suffer from concomitant structural lung disorders."

He continued, "Some of these patients had prior resection of lung lobes or even a pneumonectomy. They were left with limited reserves due to small lung volume. When weighing the benefit and potential risk of seasonal influenza vaccination for patients undergoing single-agent PD-1 or PD-L1 blockade, particularly those with lung cancer, we advise a case-by-case decision until we receive results from larger cohorts."

Egbert Smit, MD, PhD, of The Netherlands Cancer Institute, Amsterdam, concluded, "Results of this study show how much we still have to learn about the optimal use of checkpoint inhibitors in patients with lung cancer."

He continued, "The results are important, as this study was the first to investigate the impact of influenza vaccination in such patients and hinted that we place patients with lung cancer at increased risk of serious toxicities including encephalitis when we vaccinate them against influenza virus."

He added, "Until data from a larger cohort, preferably a controlled prospective study, is collected, in my institution we advocate influenza vaccination irrespective of concurrent treatment with immune checkpoint inhibitors."

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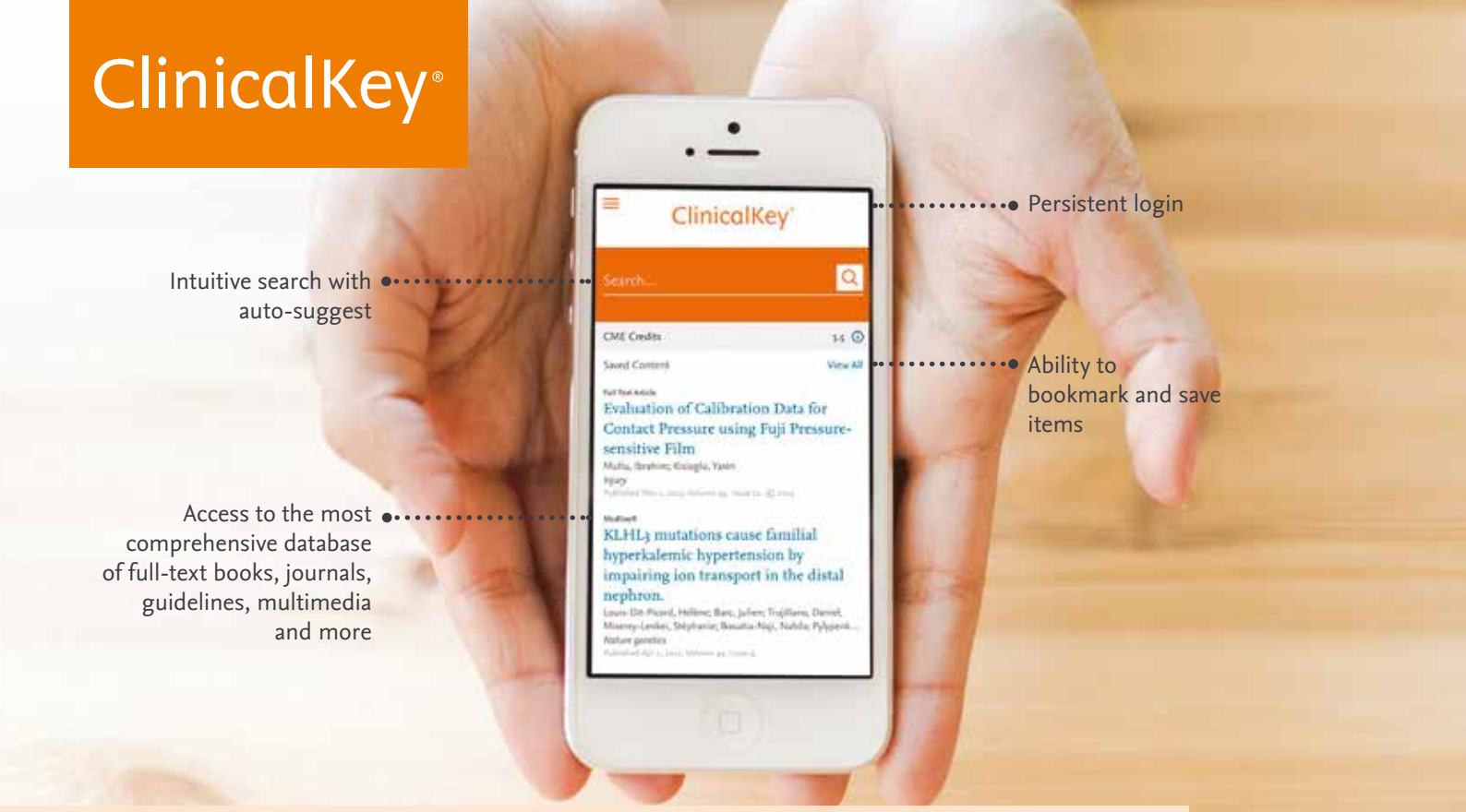

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Drugs that boost white blood cells prove safe during chemoradiotherapy of small-cell lung cancer

White blood cell-boosting drugs have proven safe during concurrent chemoradiotherapy of small-cell lung cancer, report late-breaking results of a subanalysis of the phase 3 Concurrent ONce-daily VErsus twice-daily RadioTherapy (CONVERT) trial.

Fabio Gomes, MD, of the Christie National Health Service Foundation Trust, Manchester, UK, explained "Optimal treatment for limited-stage small-cell lung cancer is concurrent chemoradiotherapy. The efficacy of this intensive treatment is balanced by more toxicity, mainly hematological but also esophageal and pulmonary. This is not a treatment for every patient and many will struggle to stay on track with the planned treatment."

Granulocyte colony-stimulating factors are commonly used supportively to boost the survival, proliferation and differentiation of neutrophils. The expected neutropenia is less severe and patients recover more quickly, reducing their risk for infectious complications.

Its use during concurrent chemoradiotherapy in small-cell lung cancer is controversial, however, and the American Society of Clinical Oncology (ASCO) recommends against its routine use. The controversy is based on results of a randomized trial of 215 patients performed between 1989 and 1991. A significant increase in severe thrombocytopenia, severe anemia, pulmonary complications, and toxic deaths was observed when granulocyte-macrophage colony-stimulating factors were used during concurrent chemoradiotherapy.

Dr Gomes said, "Two major changes have occurred since this trial was published in 1995 that may affect the safety of colony-stimulating factors in this context. First, the trial evaluated granulocyte-macrophage colony-stimulating factors, which act on more than one blood cell lineage and are not used commonly."

He continued, "Instead, we use granulocyte colony-stimulating factors, which are more specific and aim for neutrophil lineage only. Second, modern radiotherapy techniques have evolved significantly since then, are more precise, and reduce the risks of toxicity."

CONVERT randomized 547 patients with limited-stage small-cell lung cancer for concurrent chemoradiotherapy to once- or twice-daily radiotherapy. No difference in overall survival was observed between the two groups.

The protocol allowed the use of granulocyte colony-stimulating factors, and around 40% of patients received one at some point during the treatment. For the analysis presented at ELCC, toxicities and outcomes were compared between patients who received granulocyte colony-stimulating factor during concurrent chemoradiotherapy and those who did not.

They confirmed that the chance of severe thrombocytopenia or anemia during treatment nearly doubled in patients given granulocyte colony-stimulating factor to around 30% and 20%, respectively. These incidences were lower than previous reports.

Significantly higher use of further supportive measures such as platelet and blood transfusions followed. No difference in the incidence of pulmonary complications or survival was observed.

Dr Gomes said, "Granulocyte colony-stimulating factor exerted no significant negative impact on patient outcomes, a comforting result. Higher hematological toxicity was balanced by appropriate supportive care throughout treatment."

He concluded, "The use of granulocyte colony-stimulating factor during thoracic radiotherapy is safe and supports the full planned course of concurrent chemoradiotherapy to achieve the best possible benefit."

He added, "The findings should give clinicians the confidence to use granulocyte colony-stimulating factor when needed in this context. A complete analysis to be published later this year may hopefully help change current guidelines."

Stefan Zimmermann, MD, of the Hôpital Cantonal, Fribourg, Switzerland, said, "Oncologists need granulocyte colony-stimulating factor to mitigate neutropenia and increase chemotherapy delivery and compliance, but also want to see that the benefits of timely concurrent therapy outweigh the risks of toxicity."

He concluded, "In this analysis, the use of granulocyte colony-stimulating factor did not raise risk of pneumonitis, but the incidence of severe thrombocytopenia is a concern. The use of granulocyte colony-stimulating factor was not detrimental to progression-free or overall survival.

He continued, "We can conclude that primary or secondary prophylaxis of febrile neutropenia with granulocyte colony-stimulating factor is justified, but patients at higher risk of thrombocytopenia should be treated with caution."

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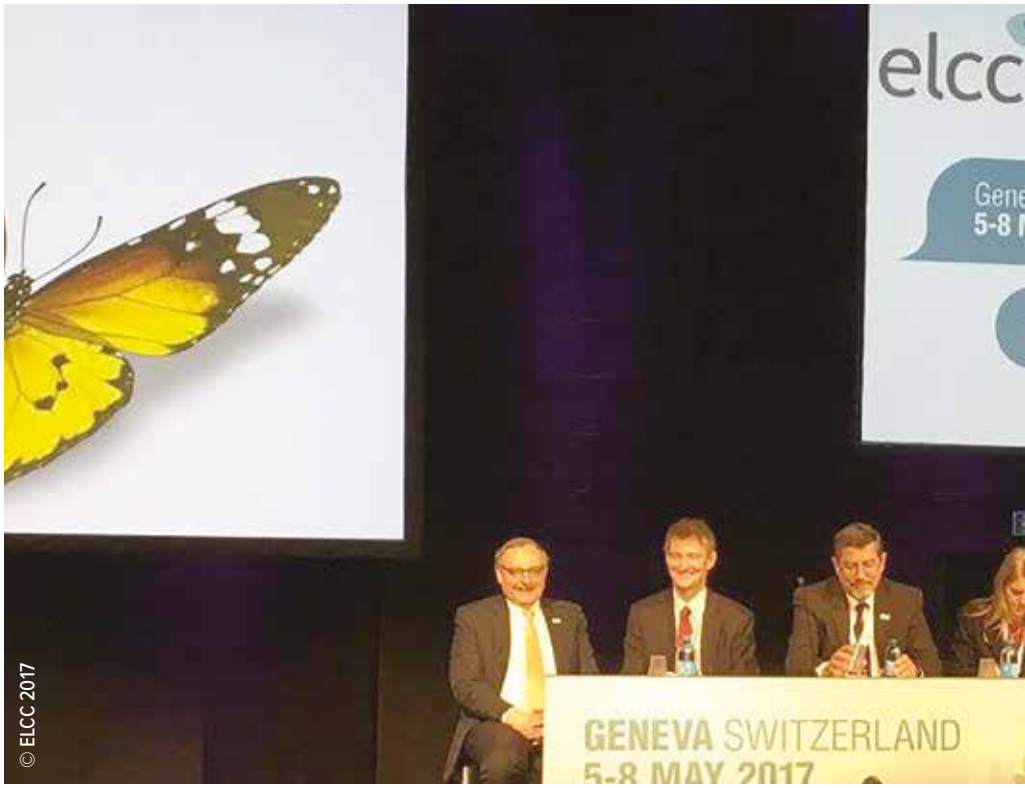

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Men require more frequent lung cancer screening than women

Men need more frequent lung cancer screening than women. The rate of non-smoking-related lung cancer differs between men and women and varies among countries. Such differences should be taken into account when considering a gender-based lung cancer screening policy.

This conclusion, based on results of a retrospective, single-center study covering nearly 47,000 patients over a 17-year period, was presented at the European Lung Cancer Conference.

Mi-Young Kim, MD, of Asan Medical Center, Seoul, South Korea, explained that the US Preventive Services Task Force recommends annual screening for lung cancer using low-dose computed tomography in adults age 55 to 80 years with a 30 pack-year smoking history who smoke or have quit within the past 15 years.

> "Results of our study suggest that the annual follow-up interval for CT is too frequent for women, and scanning every 2–3 years might be suitable. By reducing the number of unnecessary CT scans, we can decrease radiation exposure and increase cost-effectiveness.

Dr Kim said, "Less frequent screening would reduce radiation exposure but previous studies of longer screening intervals produced varied results. These varied results may have been caused by differences in the clinical and radiological presentation of lung cancer in women and men."

Dr Kim and colleagues set out to investigate sex differences in newly developed lung cancer and calculated the optimal CT screening intervals for women and men. The study included 46,766 patients who underwent chest CT screening between 2000 and 2016.

During the study period, 282 patients developed lung cancer. Of these, 186 patients were diagnosed from the initial CT scan and were excluded from the study, while 96 patients (85 men, 11 women) were diagnosed from subsequent CT scans and included in the study.

In these 96 patients, the researchers analyzed the CT screening intervals and stage and pathology of lung cancer when diagnosed, to determine whether stage and pathology differed by gender.

The average time between lung cancer being diagnosed on CT and the previous CT scan was significantly longer in women (5.6 years) than in men (3.6 years). The lung cancer stage at diagnosis, however, was higher in men: 82% of lung cancers diagnosed in women were stage I vs just 49% in men.

Pathological analyses showed that solid nodule was the most common finding in men (72%), while ground glass opacity nodule was the most common in women (45%). In men, adenocarcinoma was the most common type (42%), followed by squamous cell carcinoma (35%), small-cell lung cancer (18%), and others (5%). All women patients harbored adenocarcinoma.

Dr Kim said, "Ground glass opacity nodule is the most common feature of lung cancer in women and all cases are adenocarcinoma, so the growth rate of cancers might be low. Most female patients were nonsmokers (82%), who are at lower risk of lung cancer, while 87% of men were smokers.

All patients screened for lung cancer over a 17-year period were included, but the number of women patients was low and further studies are needed to confirm the sex differences we found."

She concluded, "Results of our study suggest that the annual follow-up interval for CT is too frequent for women, and scanning every 2–3 years might be suitable. By reducing the number of unnecessary CT scans, we can decrease radiation exposure and increase cost-effectiveness."

Pilar Garrido, MD, of Ramón y Cajal University Hospital, Madrid, Spain, commented, "Lung cancer is the most common cancer globally, but debate about the optimal screening strategy is ongoing and selection criteria are based on only age and pack-years. Several studies have highlighted that features of lung cancer differ between women and men, defining a different entity in female patients."

She continued, "Cancer incidence is expected to rise, straining limited healthcare resources further. Personalized screening strategies such as a gender approach could be a way to optimize results and allocate resources appropriately. The benefits, harms, and feasibility of implementing gender-based lung cancer screening policies should be assessed and compared with those of current recommendations."

She added, "The rate of non-smoking-related lung cancer differs between men and women and varies among countries. Such differences should be taken into account when considering a gender-based lung cancer screening policy."

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Osimertinib improves symptoms, progression-free survival in patients with advanced lung cancer

Osimertinib has been shown to improve cancer-related symptoms in patients with advanced lung cancer, conclude patient-reported outcomes from the AURA3 phase 3 clinical trial.

Chee Lee, MD, of St. George Hospital Cancer Care Centre, Kogarah, New South Wales, Australia, said, "In my experience conducting clinical trials, I often see new treatments that might be more effective, but they are usually more toxic. Osimertinib not only increased progression-free survival but was well tolerated, which makes a big difference for our patients."

AURA3 included 419 patients with advanced epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer who had progressed after first-line EGFR-tyrosine kinase inhibitor therapy. They were randomized to the oral TKI osimertinib or chemotherapy.

Patients taking osimertinib experienced significantly longer progression-free survival (10.1 months vs those who received chemotherapy (4.4 months, hazard ratio 0.30; 95% confidence interval 0.23, 0.41; $P < 0.001$).

Dr Lee presented patient-reported outcomes of AURA3. Information was collected using two standardized European Organisation for Research and Treatment of Cancer questionnaires, the Core Quality of Life Questionnaire LC13 that assessed lung cancer specific symptoms and the Core Quality of Life Questionnaire C30 that assessed general cancer symptoms.

Patients completed both questionnaires at baseline and then at regular intervals until disease progression and beyond. The researchers then analyzed the findings to determine whether symptom control was better with osimertinib vs chemotherapy.

Osimertinib reduced many lung cancer symptoms significantly, primarily appetite loss, fatigue, breathlessness, and chest pain. A trend for osimertinib to reduce cough was not statistically significant. Dr Lee said, "It took longer for symptoms to worsen in patients taking osimertinib vs chemotherapy."

In patients who experienced symptoms at the start of the study, appetite loss improved significantly faster with osimertinib than with chemotherapy, and fatigue and breathlessness improved.

Compared to chemotherapy, osimertinib significantly improved scores of global health status, physical functioning, role functioning, and social functioning. A trend toward improved emotional and cognitive function with osimertinib was not statistically significant. "Patients taking osimertinib were more able to perform normal daily activities and socialize than those taking chemotherapy," said Dr Lee.

He continued, "Patients with metastatic lung cancer receiving first-line treatment are really quite sick. Patients in AURA3 had progressed on first-line treatment and were receiving second-line therapy, so they were even sicker. To be able to reduce cancer symptoms and improve quality of life, in addition to progression-free survival, for these patients is a major leap."

Dr Lee concluded, "In patients with incurable cancer, prolonging progression-free survival only probably means little to them. Treatment that can improve symptoms and maintain quality of life as well probably means a lot to these patients."

Solange Peters, MD, of the Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, commented, "Results of AURA3 have made it clear that when patients progress on first-line targeted therapy for EGFR mutation-positive non-small-cell lung cancer with a T790M resistance mutation, they should stay on targeted therapy using a newer-generation inhibitor rather than switching to traditional chemotherapy as second-line therapy. Patients taking second-line osimertinib experienced longer progression-free survival and less toxicity than those taking chemotherapy."

She continued, "The data show that second-line osimertinib also improved time to deterioration of important lung cancer symptoms like cough, chest pain, and dyspnea significantly, and improved general health status."

"Before these results were achieved, clinicians assumed, subjectively that second-line osimertinib would be efficient and better tolerated than chemotherapy. We now have proof that the drug confers better activity and less toxicity, and improves quality of life."

Regarding the need for future studies, Dr Peters said, "Patients with EGFR mutation-positive non-small-cell lung cancer should receive frontline tyrosine kinase inhibition (first- or second-generation) and second-line osimertinib if they harbor a T790M resistance mutation. We need to determine whether options other than chemotherapy can serve as subsequent third-line therapy."

She continued, "We also need to keep in mind that osimertinib is effective only in the 55% of EGFR mutation-positive patients with non-small-cell lung cancer whose resistance to frontline tyrosine kinase inhibition is caused by this T790M gatekeeper mutation."

"More research is needed to find better second-line treatments for patients with a different mechanism of resistance, for whom chemotherapy is the only option. Finally, the opportunity for frontline osimertinib in all EGFR-mutated non-small-cell lung cancer will be described in the FLAURA trial, which is comparing first-generation tyrosine kinase inhibition vs osimertinib as initial treatment and should be reported later this year."

PracticeUpdate Editorial Team

34th Annual Miami Breast Cancer Conference

9–12 MARCH 2017 • MIAMI BEACH, FLORIDA, USA

"Lightning rounds" capped off an eventful 34th Annual Miami Breast Cancer Conference, providing a roundup of key sessions and take-aways for metastatic breast cancer presented at this year's meeting. The PracticeUpdate Editorial Team reports from Miami Beach.

CDK4/6 inhibitors in hormone receptor-positive, HER2-negative metastatic breast cancer

CDK4/6 inhibitors should be offered as first-line treatment for ER+, HER2-negative breast cancer patients since they significantly increase the time to progression when they are combined with endocrine therapy.

This was the conclusion of a talk on CDK 4/6 inhibitors in ER+ HER2-negative metastatic breast cancer at the 34th Miami Breast Cancer Conference.

Kimberly L. Blackwell, MD of Duke University Medical Center, Durham, North Carolina explained that CDK4/6 inhibitors combined with endocrine therapy have shown improvements in progression free survival.

Dr Blackwell began by reviewing the mechanism of action of CDK4/6 inhibitors and their interaction with cyclin D1 to phosphorylate the retinoblastoma tumor suppressor gene.

Dr Blackwell referred to the clinical trials that led to the FDA approval of palbociclib for patients with ER+ metastatic breast cancer.

PALOMA-1 is the phase II pivotal trial of palbociclib in combination with letrozole in first-line treatment of ER+ metastatic breast cancer that showed a 10-month improvement with the combination. The confirmatory PALOMA-2 trial was a phase 3 randomized study that enrolled 666 postmenopausal patients with ER+ metastatic breast cancer and no prior treatment for advanced disease to received either palbociclib in combination with letrozole or placebo in combination with letrozole. This trial showed that the palbociclib-letrozole group had a 10.3-month improvement in progression free survival compared to the placebo-letrozole group with a hazard ratio of 0.58 that was statistical significant. Finally, PALOMA-3 compared fulvestrant plus palbociclib versus fulvestrant plus placebo in patients with hormone receptor positive metastatic breast cancer that progressed on previous endocrine therapy. The combination doubled progression free survival.

Ribociclib is the other CDK4/6 inhibitor that has shown to improve progression free survival in combination with letrozole.

The MONALEESA-2 was a phase III clinical trial that randomized 668 postmenopausal women with hormone receptor positive, HER2-negative recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease to ribociclib in combination with letrozole versus ribociclib plus placebo. The progression free survival was significantly longer in the ribociclib group with a statistical significant hazard ratio of 0.56. With this results probably ribociclib will we approve this year.

Finally, MONARCH 1, a phase 2 single-arm study showed that the selective CDK4 and CDK6 inhibitor abemaciclib used as a single agent induced objective tumor responses as monotherapy in patients with refractory hormone receptor-positive breast cancer that have failed multiple prior therapies. Even though this study did not meet the predefined objective response rate, 42% of women had clinical benefit. Data has also shown that abemaciclib crosses the blood-brain barrier.

The toxicity profile of this agents differs in that palbociclib and ribociclib cause more neutropenia and that abemaciclib causes more abdominal pain and diarrhea. We need to refer patients to clinical trials to learn how to use them and which patient population will benefit from these agents.

PracticeUpdate Editorial Team

Lightning rounds at the 34th Annual Miami Breast Conference

The 34th Annual Miami Breast Conference took place form March 9–12 in Miami Beach. It ended on Sunday March 12th with the "Lightning rounds" providing an overview of the conference. The take home messages for metastatic breast cancer were:

Brain metastasis

- In patients with brain metastasis whole brain radiation should be avoided.
- If the only site of progression is the brain, patients should receive local therapy and systemic therapy should not be changed.

HER2+ breast cancer

- The demographics of patients with metastatic HER2+ breast cancer has changed. Higher proportion are de novo metastatic and hormone receptor positive.
- The first line treatment for metastatic HER2+ breast cancer is the combination of a Taxane with Trastuzumab and Pertuzumab. The second line is TDM-1 and many options are available for third line.

Hormone receptor positive breast cancer

- First line therapy for hormone receptor positive metastatic breast cancer has changed. Targeted combinations are superior to their monotherapy comparators.
- Novel agents in the treatment of hormone receptor positive breast cancer include mTOR inhibitors (everolimus), CDK inhibitors (palbociclib, ribociclib, abemaciclib) and PI3K inhibitors (buparlisib, taselisib).
- CDK4/6 inhibitors are here to stay. Palbociclib is approved for first and second line treatment in combination with letrozole or fulvestrant and Ribociclib will likely be approved this year in combination with letrozole.

Triple negative breast cancer

- PARP inhibitors will be an option for patients with BRCA1 or BRCA2 germline mutations.
- Olaparib met its primary endpoint in the phase III trial in BRCA-mutated metastatic breast cancer.

Immunotherapy

- Recent advances have been made in immunotherapy for metastatic breast cancer. Combination strategies are needed to enhance the immune infiltrate and their efficacy.

Androgen receptor

- Based on the encouraging phase II data, studies targeting the androgen receptor are ongoing in both estrogen receptor positive and negative breast cancer.

Diagnostics

- Assays with circulating tumor cells and circulating tumor DNA are not ready for prime time and routine use.
- Combination of biomarkers are critical to future studies.

PracticeUpdate Editorial Team

EXPERT COMMENTARY

HR+ breast cancer: current concepts from the Miami Breast Cancer Conference

Interview with Reshma L. Mahtani DO

Ana Sandoval MD, practicing hematologist/oncologist in Miami, Florida speaks with Dr Mahtani on some of the major highlights in hormone-positive metastatic breast cancer at the MBCC 2017 meeting, including treatment sequence, prevention of everolimus toxicity, and PI3K inhibitors.

Dr Sandoval: What would you consider to be the major highlights in hormone-positive metastatic breast cancer at this year's MBCC?

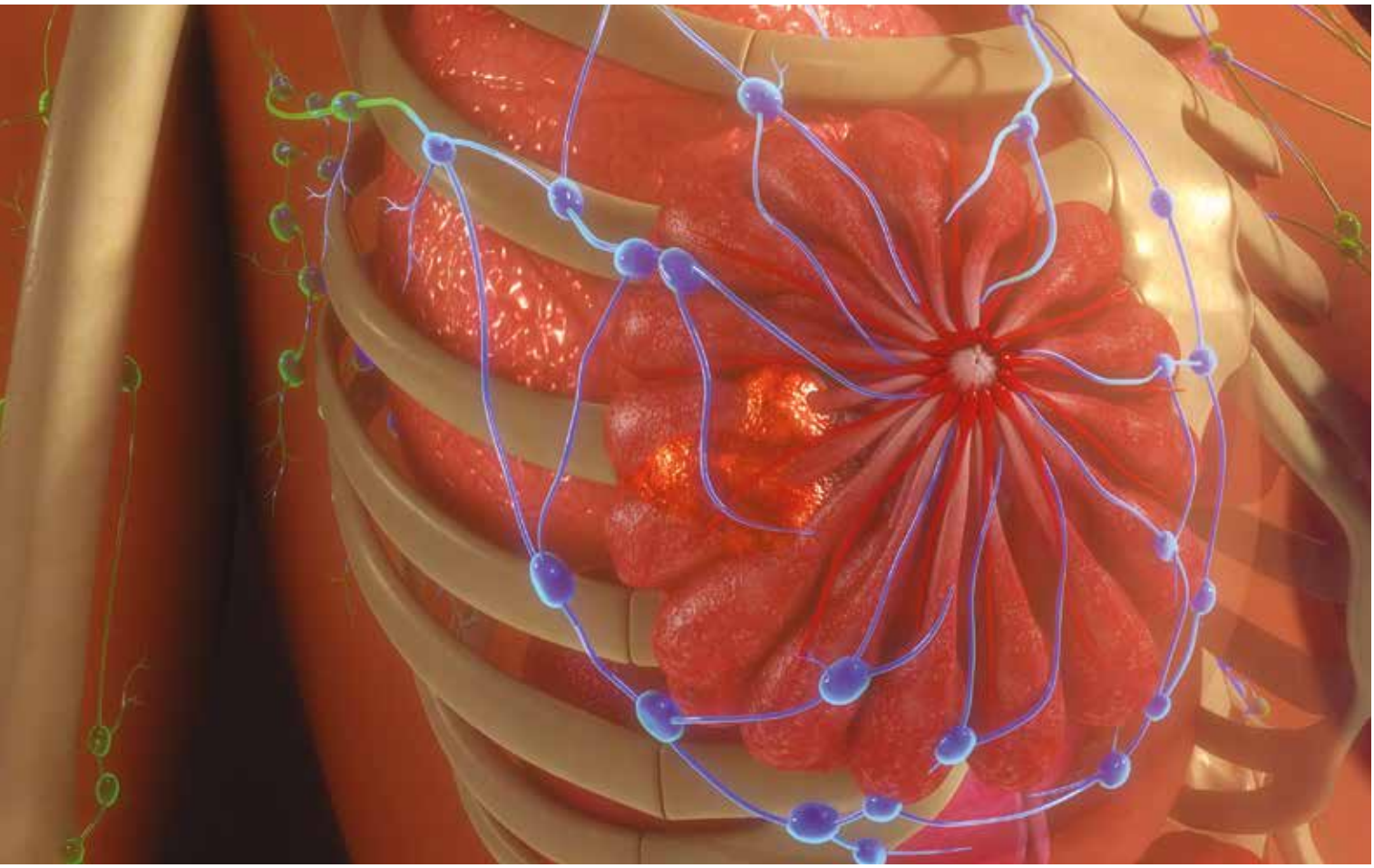
Dr Mahtani: A general theme we have heard a lot about over the last several years involves identifying pathways that mediate endocrine resistance. This year at MBCC we heard a lot of discussion about CDK4/6 inhibitors, which have really been a major addition to the armamentarium for ER+ metastatic breast cancer. Palbociclib has demonstrated impressive improvements in progression-free survival for patients treated in the first-line setting in combination with a nonsteroidal aromatase inhibitor (NSAI). It is also indicated for those who developed recurrent disease while on adjuvant hormonal therapy, or after progression on an NSAI for metastatic disease, in combination with fulvestrant. We also heard about other CDK4/6 inhibitors, including ribociclib, which was approved the day after the conference ended. Any differences in efficacy or toxicity remain to be seen. We also heard about abemaciclib, which is unique in that it has demonstrated single-agent activity in a heavily pretreated population. Finally, we heard about other novel therapies including mTOR inhibitors and PI3K inhibitors.

Dr Sandoval: What is your approach in the treatment of hormone-positive metastatic breast cancer?

Dr Mahtani: First and foremost, my approach is to recognize that, unfortunately, ER+ metastatic breast cancer is not usually a curable illness, and we have to be quite cognizant of treatment-related toxicities and how they impact a patient's quality of life. As such, I always try to exhaust hormonal therapies prior to moving to chemotherapy, if I feel this is appropriate based on disease burden and the patient's symptoms. When making treatment decisions, I try to maximize the benefit of treatments by sequencing therapies such that patients get the most time possible on a particular treatment.

Dr Sandoval: In what way do you sequence the available therapy for hormone-positive metastatic disease?

Dr Mahtani: Many patients are now receiving AIs in the adjuvant setting. For a patient who has developed recurrent disease more than 1 year post completion of an AI in



> When making treatment decisions, I try to maximize the benefit of treatments by sequencing therapies such that patients get the most time possible on a particular treatment.

the adjuvant setting, my standard approach is to start with letrozole and palbociclib, based on the PALOMA-1 and -2 data. For patients who progressed while on an adjuvant AI, I usually start with fulvestrant and palbociclib. I really don't understand the concept of "saving" this effective therapy for later, as the majority of patients do very well from a toxicity perspective and it's clearly an effective therapy. In later lines of therapy, I consider other agents such as fulvestrant monotherapy (in patients who received letrozole and palbociclib first line) or exemestane and everolimus. Of course, we can't forget some of our other hormonal therapy options such as tamoxifen, high-dose estrogen therapy, and even megestrol. Some of these are older treatments but can still be very effective. Finally, we always keep clinical trial options in mind.

Dr Sandoval: Dr Hope Rugo mentioned steroid mouthwash to prevent everolimus toxicity. Do you have any advice to manage this toxicity?

Dr Mahtani: The SWISH trial was a study that evaluated the efficacy of a steroid-based mouthwash in a preventative fashion to ameliorate one of the major toxicities of everolimus, which is stomatitis. We know this toxicity can be severe and it happens early on. It can be associated with significant weight loss and even dehydration and hospitalization. I think the important point about this toxicity is it highlights the need for us to educate our patients about how to use the mouthwash and when to hold the drug. The goal of many of our targeted therapy combinations is to delay the use of chemotherapy. Therefore, we need to learn to manage the toxicities associated with some of these therapies, so as to not take away the benefit of hormonal therapy.

Dr Sandoval: Where do you think PI3K inhibitors will likely fit into the treatment for hormone-positive metastatic breast cancer?

Dr Mahtani: The PI3K pathway is an important pathway in cancer metabolism and growth. Mutations in this pathway are common in breast cancer, with some data demonstrating PI3K is implicated in causing resistance to HER2-targeted therapies, and hormonal therapies as well. Some of the agents that have been studied are considered pan-PI3K inhibitors and have shown relatively small benefits in an unselected population. When looking at PI3K-mutant breast cancers, the magnitude of benefit is greater in certain series. However, a major concern with this class of therapy is toxicity, as many of these pan-inhibitors are associated with significant side effects such as psychiatric issues, abnormalities on liver function tests, and hyperglycemia. We will likely use these agents further down the line for ER+ metastatic disease, but hopefully we will see improved side-effect profiles with the more alpha-specific inhibitors that are also under investigation.

Dr Mahtani is a hematologist/medical oncologist practicing in south Florida, and an assistant clinical professor of hematology/oncology at the Sylvester Comprehensive Cancer Center in Miami.

Novel agents in the treatment of hormone receptor-positive metastatic breast cancer

Many new options are available for the treatment of hormone receptor-positive metastatic breast cancer.

This was the conclusion of a talk on novel agents in the treatment of hormone receptor positive metastatic breast cancer at the 34th Miami Breast Cancer Conference.

Ruth Oratz, MD clinical professor of Medicine at NUY School of medicine summarized the current options and drugs under development to treat patients with hormone receptor positive metastatic breast cancer.

She started by citing the TARGET trial that showed anastrozole was better than tamoxifen for treatment of postmenopausal woman with hormone positive metastatic breast cancer. She then mentioned the FALCON trial that was a phase 3 randomized trial that showed a significant longer progression free survival in postmenopausal woman with hormone positive metastatic breast not previously treated for their advanced disease receiving fulvestrant compared with anastrozole (16.6 versus 13.8 months).

BOLERO 2 then showed that everolimus in combination with exemestane was superior to exemestane alone (progression free survival of 7.8 vs 3.3 months) in patients with hormone positive breast cancer that progressed during or following letrozole or anastrozole. PALOMA 1 and 2 led to the approval of palbociclib as first line treatment of postmenopausal woman with hormone receptor positive metastatic breast cancer. PALOMA 3 showed that palbociclib combined with fulvestrant was better than fulvestrant alone in in patients with hormone receptor positive metastatic breast cancer that progressed on previous endocrine therapy. In 2016, the results of the PrECOG 0102 trial showed that fulvestrant in combination with everolimus doubled progression free survival in postmenopausal women with hormone receptor positive, HER2 negative metastatic breast cancer that progressed on aromatase inhibitors.

At this time the main question is how are we going to sequence the available therapy for metastatic hormone receptor positive breast cancer. Based on the prior studies an acceptable sequence would be letrozole in combination with palbociclib followed by fulvestrant in combination with everolimus.

The newest target therapies that are been studied are the PI3K inhibitors. BELLE 3 showed a modest but statistical significant improvement in progression free survival when buparlisib was added to fulvestrant in patients who had progressed after treatment with everolimus. Patients who had a PI3K mutation seemed to benefit the most. Taselisib is another agent that is currently on the pipeline.

She finalized her talk by mentioning an oral selective estrogen receptor downregulator (SERD) that is currently under development, has already been tested in healthy volunteers and has shown that is well tolerated and safe.

PracticeUpdate Editorial Team

PFS of early interim PET-positive patients with advanced-stage Hodgkin's lymphoma treated with BEACOPPescalated alone or in combination with rituximab

COMMENT

By David J Straus MD

Patients with advanced-stage Hodgkin's lymphoma treated with ABVD with a positive interim PET have decreased progression-free survival (PFS) as compared with patients whose interim PET is negative.[1] This does not appear to be true for patients who received escalated BEACOPP as demonstrated in this publication of the results of the HD18 trial of the German Hodgkin Study Group. A positive interim PET after two cycles of escalated BEACOPP using Deauville scores 3 to 5 (more than uptake in the mediastinal blood pool) was observed in 44% who were then randomized to six more cycles of escalated BEACOPP alone or with the addition of rituximab. Estimated 3-year PFS was 91.4% for escalated BEACOPP alone and 93.0% for escalated BEACOPP plus rituximab.

There are limitations to this study. The activity of rituximab in Hodgkin's lymphoma is unclear and based on limited pilot data.[2,3] Also, a lower PFS might have been found for interim PET–positive patients if more stringent criteria were used for interim PET positivity such as Deauville scores 4 to 5 (more than liver uptake), as was employed in the recently published risk-adapted S0816 and RATHL trials for advanced Hodgkin's lymphoma patients.[4,5]

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Dr Strauss is an attending physician on the Lymphoma Service in the Department of Medicine at Memorial Sloan-Kettering Cancer Center in New York.

The Lancet Oncology

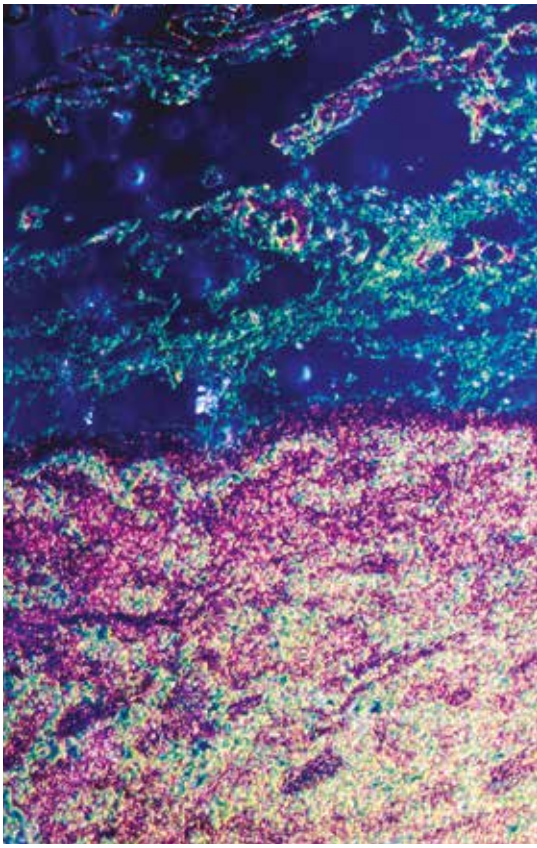
Take-home message

- This open-label, international, phase III study enrolled 440 patients with newly diagnosed, advanced-stage Hodgkin's lymphoma who had a positive interim PET after two cycles of BEACOPPescalated chemotherapy and were randomized to receive six additional courses of either BEACOPPescalated or BEACOPPescalated plus rituximab (R-BEACOPPescalated) to evaluate survival outcomes with the intensified regimen vs the standard. After a median follow-up of 33 months, the estimated 3-year progression-free survival was not significantly different in the R-BEACOPPescalated group compared with the BEACOPPescalated group (93.0% vs 91.4%, respectively). Common grade 3/4 adverse events reported in both groups were leukopenia and severe infections. In all, 6 patients in the BEACOPPescalated group and 10 patients in the R-BEACOPPescalated group died, with fatal treatment-related infections occurring in 1 and 3 patients, respectively.
- Adding rituximab to BEACOPPescalated did not lengthen progression-free survival compared with the standard BEACOPP escalated in patients with newly diagnosed, advanced-stage Hodgkin's lymphoma who had a positive interim PET scan, suggesting that interim PET cannot identify patients at high risk for treatment failure in this population.

Abstract

BACKGROUND Advanced stage Hodgkin's lymphoma represents a heterogeneous group of patients with different risk profiles. Data suggests that interim PET assessment during chemotherapy is superior to baseline international prognostic scoring in terms of predicting long-term treatment outcome in patients with Hodgkin's lymphoma. We therefore hypothesised that early interim PET-imaging after two courses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) might be suitable for guiding treatment in patients with advanced stage Hodgkin's lymphoma. We aimed to assess whether intensifying standard chemotherapy (BEACOPPescalated) by adding rituximab would improve progression-free survival in patients with positive PET after two courses of chemotherapy.

METHODS In this open-label, international, randomised, phase 3 study, we recruited patients aged 18–60 years with newly diagnosed, advanced stage Hodgkin's lymphoma from 160 hospitals and 77 private practices in Germany, Switzerland, Austria, the Netherlands, and the Czech Republic. Interim PET-imaging was done after two cycles of BEACOPPescalated and centrally assessed by an expert panel. Patients with a positive PET after 2 cycles of BEACOPPescalated chemotherapy (PET-2) were randomly assigned (1:1) to receive six additional courses of either BEACOPPescalated (BEACOPPescalated group) or BEACOPPescalated plus rituximab (R-BEACOPPescalated group). PET-2 was assessed using a 5-point scale with (18)FDG uptake higher than the mediastinal blood pool (corresponding to Deauville scale 3) defined as positive. BEACOPPescalated was given as previously described; rituximab was given intravenously at a dose of 375 mg/m^2 (maximum total

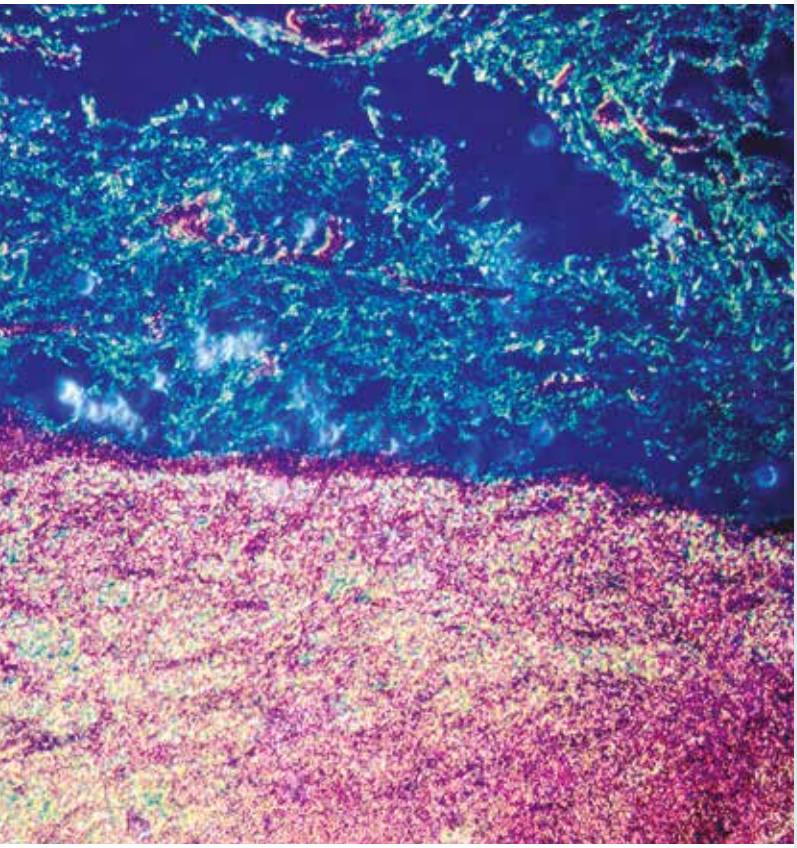


dose 700 mg), the first administration starting 24 h before starting the fourth cycle of BEACOPPescalated (day 0 and day 3 in cycle 4, day 1 in cycles 5-8). Randomisation was done centrally and used the minimisation method including a random component, stratified according to centre, age, stage, international prognostic score, and sex. The primary efficacy endpoint was 5 year progression-free survival, analysed in the intention-to-treat population. We are reporting this second planned interim analysis as the final report of the trial.

FINDINGS Between May 14, 2008, and May 31, 2011, we enrolled 1100 patients. 440 patients had a positive PET-2 and were randomly assigned to either the BEACOPPescalated group (n=220) or the R-BEACOPPescalated group (n=220). With a median follow-up of 33 months (IQR 25–42) for progression-free survival, estimated 3 year progression-free survival was 91.4% (95% CI 87.0–95.7) for patients in the BEACOPPescalated group and 93.0% (89.4–96.6) for those in the R-BEACOPPescalated group (difference 1.6%, 95% CI -4.0 to 7.3; log rank p=0.99). Common grade 3–4 adverse events were leucopenia (207 [95%] of 218 patients in the BEACOPPescalated group vs 211 [96%] of 220 patients in the R-BEACOPPescalated group), and severe infections (51 [23%] vs 43 [20%] patients). Based on a futility analysis, the independent data monitoring committee recommended publication of this second planned interim analysis as the final result. Six (3%) of 219 patients in the BEACOPPescalated group and ten (5%) of 220 in the R-BEACOPPescalated group died; fatal treatment-related toxic effects occurred in one (<1%) patient in the BEACOPPescalated group and three (1%) in the R-BEACOPPescalated group, all of them due to infection.

INTERPRETATION The addition of rituximab to BEACOPPescalated did not improve the progression-free survival of PET-2 positive patients with advanced stage Hodgkin's lymphoma. However, progression-free survival for PET-2 positive patients was much better than expected, exceeding even the outcome of PET-2-unselected patients in the previous HD15 trial. Thus, PET-2 cannot identify patients at high-risk for treatment failure in the context of the very effective German Hodgkin Study Group standard treatment for advanced stage Hodgkin's lymphoma.

Progression-free survival of early interim PET-positive patients with advanced stage Hodgkin's lymphoma treated with BEACOPPescalated alone or in combination with rituximab (HD18): an open-label, international, randomised phase 3 study by the German Hodgkin Study Group. *Lancet Oncol* 2017 Feb 21;[EPub Ahead of Print], P Borchmann, H Haverkamp, A Lohri, et al.



Lenalidomide maintenance therapy in elderly patients with diffuse large B-cell lymphoma

Journal of Clinical Oncology

Take-home message

- This randomized phase III trial compared the efficacy of maintenance therapy with lenalidomide versus placebo in 650 elderly patients with diffuse large B-cell lymphoma (DLBCL) following a complete or partial response to treatment with R-CHOP. Maintenance therapy with lenalidomide did not reach a median PFS vs 58.9 months achieved with placebo (HR, 0.708; P = 0.01). The improved PFS was maintained in subgroup analysis for gender, age, age-adjusted IPI, response to R-CHOP, and PET status at assignment. OS was similar between the two treatment arms at a median follow-up of 52 months (HR, 1.218). In the lenalidomide versus placebo arms, the most common grade ≥3 adverse events were neutropenia at 56% and 22%, respectively, and cutaneous reactions at 5% and 1%, respectively.
- In elderly patients with DLBCL who achieved a complete or partial response to R-CHOP, 24 months of lenalidomide maintenance therapy significantly prolonged PFS.

Abstract

PURPOSE The standard treatment of patients with diffuse large B-cell lymphoma (DLBCL) is rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Lenalidomide, an immunomodulatory agent, has shown activity in DLBCL. This randomized phase III trial compared lenalidomide as maintenance therapy with placebo in elderly patients with DLBCL who achieved a complete response (CR) or partial response (PR) to R-CHOP induction.

METHODS Patients with previously untreated DLBCL or other aggressive B-cell lymphoma were 60 to 80 years old, had CR or PR after six or eight cycles of R-CHOP, and were randomly assigned to lenalidomide maintenance 25 mg/d or placebo for 21 days of every 28-day cycle for 24 months. The primary end point was progression-free survival (PFS).

RESULTS A total of 650 patients were randomly assigned. At the time of the primary analysis (December 2015), with a median follow-up of 39 months from random assignment, median PFS was not reached for lenalidomide maintenance versus 58.9 months for placebo (hazard ratio, 0.708; 95% CI, 0.537 to 0.933; P = 0.01). The result was consistent among analyzed subgroups (eg, male v female, age-adjusted International Prognostic Index 0 or 1 v 2 or 3, age younger than 70 v ≥ 70 years), response (PR v CR) after R-CHOP, and positron emission tomography status at assignment (negative v positive). With longer median follow-up of 52 months (October 2016), overall survival was similar between arms (hazard ratio, 1.218; 95% CI, 0.861 to 1.721; P = 0.26). Most common grade 3 or 4 adverse events associated with lenalidomide versus placebo maintenance were neutropenia (56% v 22%) and cutaneous reactions (5% v 1%), respectively.

CONCLUSION Lenalidomide maintenance for 24 months after obtaining a CR or PR to R-CHOP significantly prolonged PFS in elderly patients with DLBCL.

Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol* 2017 Apr 20;[EPub Ahead of Print], C Thieblemont, H Tilly, M Gomes da Silva, et al.

Reduced-dose radiotherapy for HPV-associated squamous cell carcinoma of the oropharynx

The Lancet Oncology

Take-home message

- This single-arm, phase II trial investigated the efficacy of chemoradiotherapy with reduced-dose radiation in patients with HPV-positive oropharyngeal carcinoma. Following induction therapy, patients with a complete or partial response (55%) received 54 Gy, or 60 Gy if they had a less than partial or no response (45%). At 2 years, PFS was 92%. Grade 3 adverse events occurred in 39% of patients, including leucopenia (39%) and neutropenia (11%) during induction therapy and mucositis (9%) and dysphagia (9%) during chemoradiotherapy. None of the patients was dependent on a gastrostomy 6 months after treatment.
- In patients with HPV-positive oropharyngeal carcinoma, a 15% to 20% reduction in radiation doses during chemoradiotherapy was associated with a high PFS and improved toxicity compared with standard doses.

Abstract

BACKGROUND Head and neck cancers positive for human papillomavirus (HPV) are exquisitely radiosensitive. We investigated whether chemoradiotherapy with reduced-dose radiation would maintain survival outcomes while improving tolerability for patients with HPV-positive oropharyngeal carcinoma.

METHODS We did a single-arm, phase 2 trial at two academic hospitals in the USA, enrolling patients with newly diagnosed, biopsy-proven stage III or IV squamous-cell carcinoma of the oropharynx, positive for HPV by p16 testing, and with Zubrod performance status scores of 0 or 1. Patients received two cycles of induction chemotherapy with 175 mg/m^2 paclitaxel and carboplatin (target area under the curve of 6) given 21 days apart, followed by intensity-modulated radiotherapy with daily image guidance plus 30 mg/m(2) paclitaxel per week concomitantly. Complete or partial responders to induction chemotherapy received 54 Gy in 27 fractions, and those with less than partial or no responses received 60 Gy in 30 fractions. The primary endpoint was progression-free survival at 2 years, assessed in all eligible patients who completed protocol treatment.

FINDINGS Between Oct 4, 2012, and March 3, 2015, 45 patients were enrolled with a median age of 60 years (IQR 54–67). One patient did not receive treatment and 44 were included in the analysis. 24 (55%) patients with complete or partial responses to induction chemotherapy received 54 Gy radiation, and 20 (45%) with less than partial responses received 60 Gy. Median follow-up was 30 months (IQR 26–37). Three (7%) patients had locoregional recurrence and one (2%) had distant metastasis; 2-year progression-free survival was 92% (95% CI 77–97). 26 (39%) of 44 patients had grade 3 adverse events, but no grade 4 events were reported. The most common grade 3 events during induction chemotherapy were leucopenia (17 [39%]) and neutropenia (five [11%]), and during chemoradiotherapy were dysphagia (four [9%]) and mucositis (four [9%]). One (2%) of 44 patients was dependent on a gastrostomy tube at 3 months and none was dependent 6 months after treatment.

INTERPRETATION Chemoradiotherapy with radiation doses reduced by 15–20% was associated with high progression-free survival and an improved toxicity profile compared with historical regimens using standard doses. Radiotherapy de-escalation has the potential to improve the therapeutic ratio and long-term function for these patients.

Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study. *Lancet Oncol* 2017 Apr 20;[EPub Ahead of Print], AM Chen, C Felix, PC Wang, et al.

Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer

Journal of Clinical Oncology

Take-home message

- The authors of this single-arm, phase II study evaluated the suitability of pembrolizumab for the treatment of platinum- and cetuximab-refractory head and neck cancer. Among 171 treated patients, the overall response rate was 16%, with a median duration of response of 8 months. Adverse events occurred in 64% of patients; 15% of patients experienced an adverse event of grade ≥3. Median progression-free survival was 2.1 months, whereas median overall survival was 8 months.
- The study authors conclude that pembrolizumab demonstrates clinically meaningful antitumor activity within this clinical context, with an acceptable safety profile given the recurrent/metastatic and refractory nature of the disease.

Abstract

PURPOSE There are no approved treatments for recurrent/metastatic head and neck squamous cell carcinoma refractory to platinum and cetuximab. In the single-arm, phase II KEYNOTE-055 study, we evaluated pembrolizumab, an anti–programmed death 1 receptor antibody, in this platinum- and cetuximab-pretreated population with poor prognosis.

METHODS Eligibility stipulated disease progression within 6 months of platinum and cetuximab treatment. Patients received pembrolizumab 200 mg every 3 weeks. Imaging was performed every 6 to 9 weeks. Primary end points: overall response rate (Response Evaluation Criteria in Solid Tumors v1.1, central review) and safety. Efficacy was assessed in all dosed patients and in subgroups on the basis of programmed death ligand 1 (PD-L1) expression and human papillomavirus (HPV) status.

RESULTS Among 171 patients treated, 75% received two or more prior lines of therapy for metastatic disease, 82% were PD-L1 positive, and 22% were HPV positive. At the time of analysis, 109 patients (64%) experienced a treatment-related adverse event; 26 patients (15%) experienced a grade ≥ 3 event. Seven patients (4%) discontinued treatment, and one died of treatment-related adverse events. Overall response rate was 16% (95% CI, 11% to 23%), with a median duration of response of 8 months (range, 2+ to 12+ months); 75% of responses were ongoing at the time of analysis. Response rates were similar in all HPV and PD-L1 subgroups. Median progression-free survival was 2.1 months, and median overall survival was 8 months.

CONCLUSION Pembrolizumab exhibited clinically meaningful antitumor activity and an acceptable safety profile in recurrent/metastatic head and neck squamous cell carcinoma previously treated with platinum and cetuximab.

Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase ii study. *J Clin Oncol* 2017 Mar 22;[EPub Ahead of Print], J Bauml, TY Seiwert, DG Pfister, et al.

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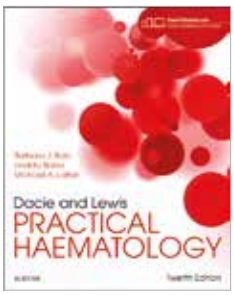

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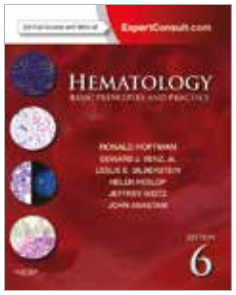

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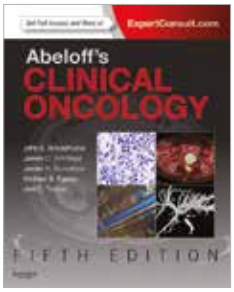

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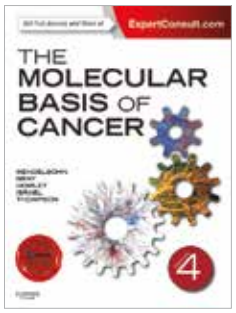

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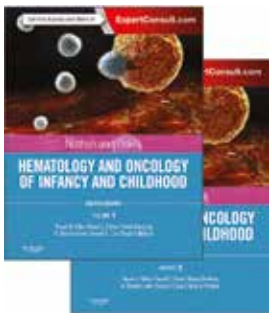

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Abiraterone acetate for metastatic prostate cancer patients with suboptimal response to hormone induction

JAMA Oncology

Take-home message

- This phase II study investigated the efficacy of abiraterone acetate with prednisone in 40 men with metastatic prostate cancer who had a suboptimal response to initial androgen-deprivation therapy and PSA levels ≥4 ng/mL. After 12 months of treatment, 13% of patients achieved a PSA level ≤0.2 ng/mL, and an additional 33% achieved a partial response PSA (>0.2 and ≤4.0 ng/mL). There were no changes in PSA levels in 40% of patients, and 15% could not be assessed. Median PFS and OS were 17.5 and 25.8 months, respectively. Grade 4 adverse events included 1 case of rectal hemorrhage and 1 case of alanine aminotransferase level elevation. Grade 3 adverse events were reported by 11 patients.
- In men with advanced prostate cancer, treatment with abiraterone acetate plus prednisone was well-tolerated, and its effect on OS and PFS were promising, although only 5 men achieved the prescribed level of PSA response.

> "Unfortunately, I don't think that this trial is going to have a huge impact on how these patients are managed.

Abstract

IMPORTANCE Men with metastatic prostate cancer who have a poor response to initial androgen-deprivation therapy (ADT), as reflected by a prostate-specific antigen (PSA) level higher than 4.0 ng/mL after 7 months of ADT, have a poor prognosis, based on historical controls.

OBJECTIVE To determine the efficacy of abiraterone acetate with prednisone in these high-risk patients with a suboptimal response to hormonal induction.

DESIGN, SETTING, AND PARTICIPANTS A phase 2 single-arm study was conducted through the National Clinical Trials Network-Southwest Oncology Group. Eligible patients had metastatic prostate cancer and a PSA level higher than 4.0 ng/mL between 6 and 12 months after starting ADT. The PSA level could be rising or falling at the time of enrollment, but had to be higher than 4.0 ng/mL. No previous chemotherapy or secondary hormonal therapies were allowed, except in patients receiving a standard, first-generation antiandrogen agent with a falling PSA level at the time of enrollment; this therapy was continued in this cohort. Abiraterone acetate, 1000 mg, once daily with prednisone, 5 mg, twice daily was administered to all participants.

A total of 41 men were enrolled between the trial's activation on August 9, 2011, and closure on August 1, 2013. Data analysis was conducted from March 21 to November 29, 2016.

INTERVENTIONS Abiraterone acetate, 1000 mg, once daily by mouth with prednisone, 5 mg, by mouth twice daily.

MAIN OUTCOMES AND MEASURES The primary end point was a PSA level of 0.2 ng/mL or lower within 12 months of starting abiraterone acetate plus prednisone. A partial response (PR) was a secondary end point, defined as a PSA level reduction to lower than 4.0 ng/mL but higher than 0.2 ng/mL.

RESULTS Of the 41 men enrolled, 1 did not receive any protocol treatment and was excluded from analysis. The median (range) age of the 40 participants was 66 (39–85) years. Five (13%) patients achieved a PSA level of 0.2 ng/mL or lower (95% CI, 4–27%). Thirteen (33%) additional patients achieved a partial response, with a reduction in the PSA level to lower than 4.0 ng/mL but higher than 0.2 ng/mL. Sixteen (40%) patients had no PSA response and 6 (15%) were not assessable and assumed to be nonresponders. The median progression-free survival was 17.5 months (95% CI, 8.6–25.0 months) and the median overall survival was 25.8 months (95% CI, 15.7–25.8 months). There was 1 incident each of grade 4 adverse events of alanine aminotransferase level elevation and rectal hemorrhage. Eleven patients reported grade 3 adverse events.

CONCLUSIONS AND RELEVANCE This study did not reach its prescribed level of 6 PSA responses of 0.2 ng/mL or lower, although 5 responses were observed. The overall survival and progression-free survival rates observed in this trial are encouraging compared with historical controls. The therapy was generally well tolerated, without any clear signal of any unexpected adverse effects.

Abiraterone acetate for metastatic prostate cancer in patients with suboptimal biochemical response to hormone induction. *JAMA Oncol* 2017 Mar 30;[EPub Ahead of Print], TW Flaig, M Plets, MH Hussain, et al.

COMMENT

By Brian E Lewis MD, MPH

In this study, men with metastatic prostate cancer who had a PSA of >4.0 ng/mL when measured between 6 and 12 months of starting ADT were initiated on 1000 mg of abiraterone acetate with prednisone. The primary endpoint of the trial was the number of men who achieved a PSA of ≤0.2 ng/mL (complete response), or PSA of <4.0 ng/mL but >0.2 ng/mL (partial response). The median PSA at study entry was 23.6, and the majority (75%) of men had Gleason 8–10 prostate cancer. A total of 85% of the men had a rising PSA at study entry, which seems to indicate that most men on the trial had developed early castrate-resistant disease. In this study of 41 men who failed to achieve a PSA of <4.0 ng/mL, only 13% achieved a PSA of <0.2 ng/mL with the addition of abiraterone acetate and prednisone.

Unfortunately, I don't think that this trial is going to have a huge impact on how these patients are managed. Since early utilization of docetaxel in the setting of metastatic hormone-sensitive prostate cancer improves overall survival; the majority of patients in this study would likely have been treated with upfront chemotherapy. Also, it seems that many men in the study had developed early castrate resistance and were started on therapy in the setting of mCRPC in which abiraterone acetate is indicated.

Dr Lewis is an Assistant Professor of Clinical Medicine in the Department of Hematology and Medical Oncology at Tulane University School of Medicine in New Orleans.

Clinical calculator for early mortality in metastatic colorectal cancer

Journal of Clinical Oncology

Take-home message

- To identify factors associated with early mortality, this study analyzed pooled data from 22,654 patients with metastatic colorectal cancer from 28 randomized phase III trials. Based on multivariable logistic regression models, 30-, 60-, and 90-day mortality rates were 1.4%, 3.4%, and 5.5%, respectively. Baseline factors associated with an increased likelihood of early mortality included several laboratory parameters, lower body mass index, advanced age, BRAF-mutant status, poorer performance status, and increased number of metastatic sites. A multivariable nomogram for 90-day mortality showed good calibration across risk groups, strong internal discrimination, and good overall and within subgroup accuracy during validation with an external dataset.
- The authors have developed and validated a nomogram to determine the risk of mortality during early treatment of metastatic colorectal cancer.

Abstract

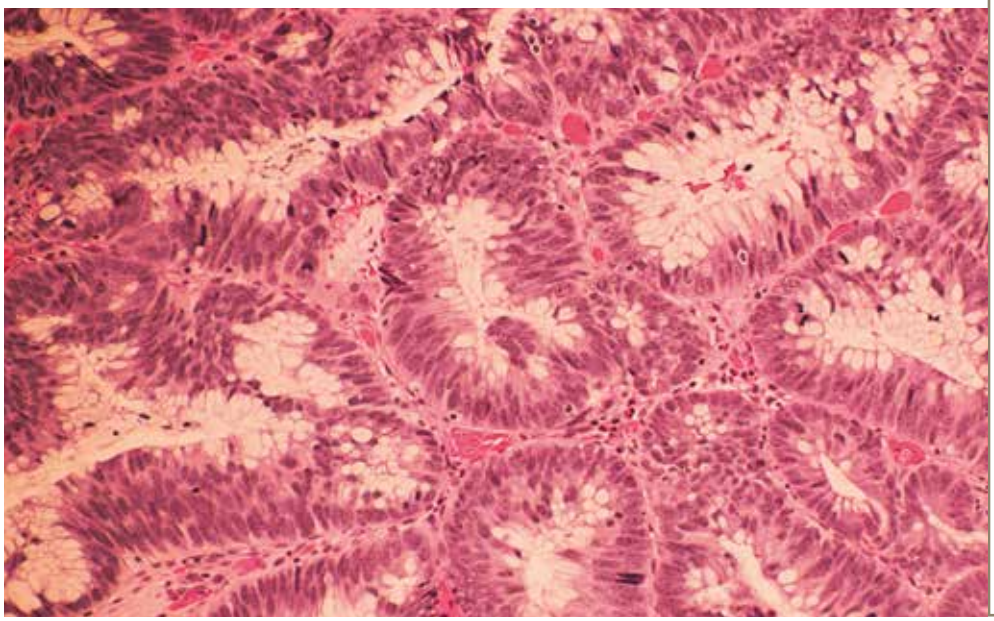
PURPOSE Factors contributing to early mortality after initiation of treatment of metastatic colorectal cancer are poorly understood.

MATERIALS AND METHODS Data from 22,654 patients enrolled in 28 randomized phase III trials contained in the ARCAD (Aide et Recherche en Cancérologie Digestive) database were pooled. Multivariable logistic regression models for 30-, 60-, and 90-day mortality were constructed, including clinically and statistically significant patient and disease factors and interaction terms. A calculator (nomogram) for 90-day mortality was developed and validated internally using bootstrapping methods and externally using a 10% random holdout sample from each trial. The impact of early progression on the likelihood of survival to 90 days was examined with time-dependent Cox proportional hazards models.

RESULTS Mortality rates were 1.4% at 30 days, 3.4% at 60 days, and 5.5% at 90 days. Among baseline factors, advanced age, lower body mass index, poorer performance status, increased number of metastatic sites, BRAF mutant status, and several laboratory parameters were associated with increased likelihood of early mortality. A multivariable model for 90-day mortality showed strong internal discrimination (C-index, 0.77) and good calibration across risk groups as well as accurate predictions in the external validation set, both overall and within patient subgroups.

CONCLUSION A validated clinical nomogram has been developed to quantify the risk of early death for individual patients during initial treatment of metastatic colorectal cancer. This tool may be used for patient eligibility assessment or risk stratification in future clinical trials and to identify patients requiring more or less aggressive therapy and additional supportive measures during and after treatment.

Clinical calculator for early mortality in metastatic colorectal cancer: an analysis of patients from 28 clinical trials in the Aide et Recherche en Cancérologie Digestive Database. *J Clin Oncol* 2017 Apr 17;[EPub Ahead of Print], LA Renfro, RM Goldberg, A Grothey, et al.



COMMENT

By Axel Grothey MD

In spite of the obvious advances in the medical management of metastatic colorectal cancer (mCRC) in recent years, a small subgroup of patients will still die early while on therapy. It is evident that some patients might be diagnosed at a very advanced, terminal stage with reduced performance status so that medical therapy might not be indicated anymore. It is difficult to assess how many patients with newly diagnosed mCRC might fall into this category. The current analysis, however, evaluated patients who were all enrolled in clinical trials, meaning that they met the inclusion criteria for participation in prospective studies. Even in this group of patients, a small, but real, early mortality rate can be found.

The parameter "60-day all-cause mortality" was initially used to describe outcomes of patients given treatment regimens that incorporated irinotecan and oxaliplatin added to a fluoropyrimidine backbone. In 2000, when IFL (bolus 5-FU/LV plus irinotecan) became the standard first-line therapy in the US, the 60-day mortality rate associated with this regimen was found to be 4% to 6%, in contrast to the 2% to 3% early mortality associated with FOLFIRI (infusion 5-FU/LV plus irinotecan). For FOLFOX, an even lower early mortality rate was found, around 1% to 2%. The standard "Mayo Clinic regimen," which relied completely on bolus 5-FU/LV injections, showed a 60-day all-cause mortality of 7% to 10%! The reason for the high early mortality rate with IFL and the Mayo Clinic regimen are twofold. Both regimens are associated with higher toxicity than more modern regimens like FOLFIRI and FOLFOX. On the other hand, they are also not as active in terms of antitumor activity, so that early deaths due to rapidly progressive disease can occur more frequently.

Dr Grothey is a consultant in the Division of Medical Oncology, Department of Oncology, at Mayo Clinic.

Managing mineralocorticoid excess in mCRPC: data review and clinical recommendations

Interview with Neeraj Agarwal MD

Dr Agarwal, a specialist in genitourinary cancer, is Associate Professor of Medicine in the Division of Oncology at the University of Utah School of Medicine in Salt Lake City, where he is also the Director of the Genitourinary Oncology Program.

Farzanna Haffizulla MD, FACP, FAWMA, who practices general internal medicine in Davie, Florida, discusses Dr Agarwal's work with eplerenone in managing mineralocorticoid excess in mCRPC.

Dr Haffizulla: Dr Agarwal, you have previously published work related to eplerenone in managing mineralocorticoid excess in patients with metastatic castration-resistant prostate cancer after they receive abiraterone. Can you tell us a little bit more about the rationale for some of this work?

Dr Agarwal: Absolutely. Abiraterone, as we know, is approved by FDA to be used along with prednisone. That's how most of the abiraterone trials were done. However, many patients have concerns about long-term use of prednisone, which is a corticosteroid, as you know. Patients who have received prior immunotherapy drugs, they're also very concerned about using corticosteroids for a long time, so why we use prednisone with abiraterone is because abiraterone can cause increased mineralocorticoids, such as aldosterone, causing fluid retention, low potassium, hypertension, and so on.

So, how could we have avoided prednisone and still block these side effects. The answer is use a drug which can antagonize high aldosterone, which is eplerenone. The advantage of eplerenone over more traditional antagonists for aldosterone, such as spironolactone, is that it is a nonsteroidal antagonist, so in theory it doesn't stimulate prostate cancer cells. So, I think that was the rationale behind using eplerenone with abiraterone. And we saw that it was very safe, and we were able to avoid prednisone in these patients. I think it's a very attractive option for our patients to be able to use abiraterone without using prednisone.

Dr Haffizulla: That's a wonderful option, absolutely. Well, I want to thank you so much for sharing your expertise, and perspective, and for bringing all of this vital information to us at PracticeUpdate.

Dr Haffizulla practices general internal medicine in Davie, Florida, within her own internal medicine concierge practice.

Management of aggressive prostate cancer variants

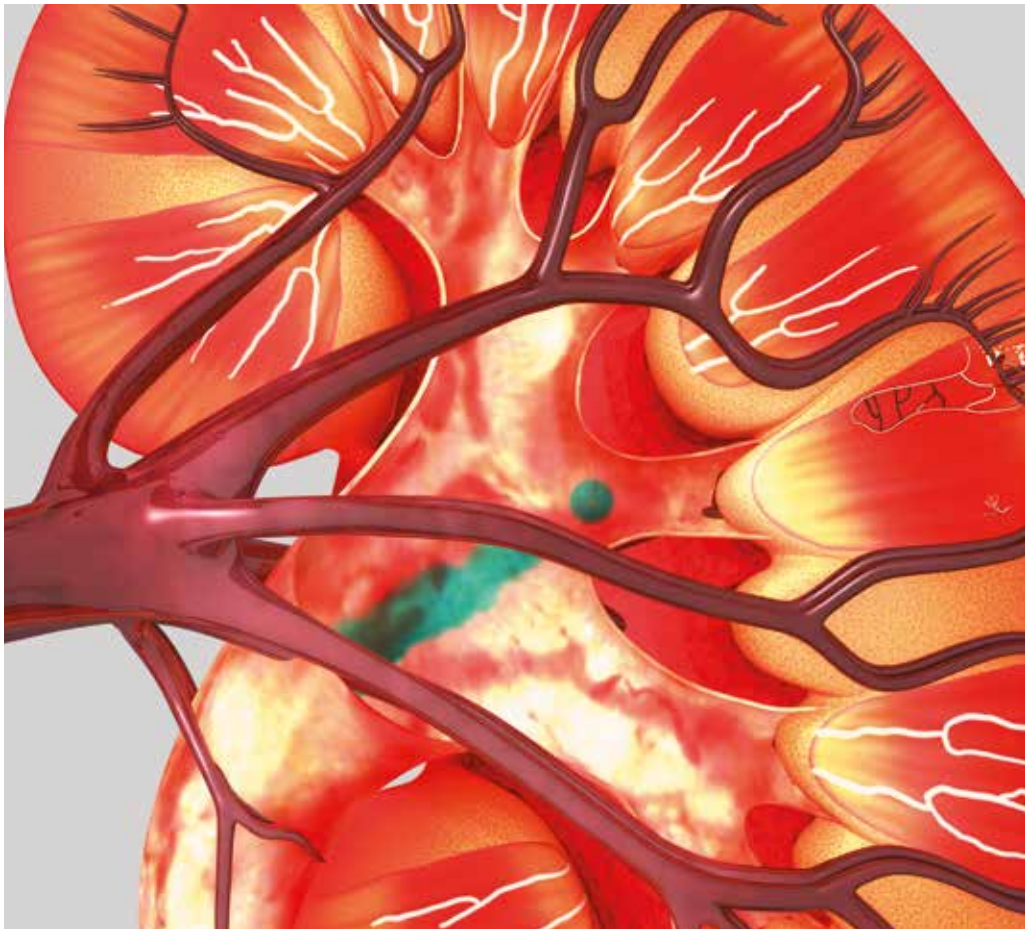
Ana Aparicio MD, Associate Professor at the University of Texas MD Anderson Cancer Centre, shares her management strategies for aggressive prostate cancer.

Go to www.practiceupdate.com to watch the full interview.

Evidence-based recommendations for second-line RCC treatment

Interview with Tanya B Dorff MD

Dr Dorff is Assistant Professor of Clinical Medicine, USC Norris Comprehensive Cancer Center and Hospital, University of Southern California, Los Angeles, California.



Farzanna Haffizulla MD, FACP, FAWMA speaks with Dr Dorff on second line treatments for renal cell carcinoma, patients who would benefit from a TKI vs PD-1 inhibitor, and approach to patients who are not benefitting from first-line therapies.

Dr Haffizulla: I would love to hear your experience on second-line treatments in renal cell carcinoma. How does this correlate with the data now?

Dr Dorff: So, there has been an explosion of new therapeutic options, which makes the landscape very complicated. Our institution still uses high-dose interleukin-2 as first-line therapy in a very select group of patients, and so for those folks, second-line therapy becomes one of the VEGF-TKIs, pazopanib or sunitinib. However, for most patients that's not really possible and so we start with the sunitinib or pazopanib and then it's a big question what's going to be the right choice in second line. So, for many patients, they are ready for a break from the daily TKI kinds of side effects, and so there's a lot of appeal to immunotherapy.

I also feel that earlier in their disease process, when they have maybe a lower volume, less symptomatic, is a better time to use immunotherapy because you can have some delay to response. You get some early responders too, for sure, but there are patients where you have to wait a bit before you see the response. There are patients, however, whose lifestyle doesn't work with coming in every 2 weeks, or maybe who didn't have so many side effects, or have bone predominant disease where cabozantinib is very appealing, so different patients will end up choosing differently, but I use cabozantinib also quite a bit in the second line.

Dr Haffizulla: I see. Now, can you just delineate clearly for us, at least from your own clinical practice in renal cell carcinoma patients, which specific patient populations would benefit from a TKI versus a PD-1 inhibitor.

Dr Dorff: Well, certainly, most renal cell patients will benefit from a TKI. There are really sound biologic underpinnings for VEGF-targeted therapy. The response rates are higher and so every renal cell cancer patient whose clear cell should absolutely get a VEGF-TKI, whether it ends up being first and second or first and third, more and more patients, I hope, are seeing multiple lines of therapy. The non-clear cell patients are a little bit more of a challenging population, and there are actually some abstracts at this meeting, showing efficacy of cabozantinib in that population. There's also one on PD-1 therapy in that population, and so I think that's been an unmet need that, hopefully, we'll get better clarity on.

Dr Haffizulla: Absolutely. Now, we talked about second-line therapy. I want to hear your summary or your algorithm in mind, or your approach to patients in whom first-line therapies are proving ineffective.

Dr Dorff: So, for patients who are symptomatic or rapidly progressing, I'm going to reach for another VEGF-TKI, such as cabozantinib because they really need to get relief in the short term. You could also reach for lenvatinib/everolimus in that population, and there are times where that may be the right fit for your patient. But generally speaking, if someone's had a really good response to a VEGF-TKI or if they have a low disease burden to start out with, and now they're slowly progressing, then, again, I typically will go for the PD-1 therapy provided that the patient agrees that they can commit to that.

Dr Haffizulla: Well, I want to thank you for providing such vital information, and for clearly laying it out for our clinicians and practitioners who are viewing this piece.

Dr Dorff: Thanks.

Role of microsatellite instability in solid tumors: clinical implications

By Erin Schenk MD, PhD

Dr Schenk is a hematology/oncology fellow in the Clinician-Investigator Training Program at Mayo Clinic.

The fidelity of the human genome is maintained by multiple pathways of DNA repair that respond to DNA damage or errors in replication.[1] Mismatch repair (MMR) proteins proofread newly replicated DNA strands for mistakes in base pairing and small deletions or insertions of nucleotides that occur during DNA replication due to template strand slippage.[2,3] When an error is found, the MMR protein complex excises the incorrect nucleotides and the resulting gap is repaired.[4] It is estimated that MMR proteins improve the accuracy of DNA replication by several orders of magnitude.[5]

Mutations of a principal MMR protein can result in the accumulation of DNA errors, which are compounded by subsequent cycles of DNA replication.[6] Repetitive elements within the genome are especially sensitive to MMR protein dysfunction and the gain or loss of nucleotide repeats within these repetitive elements is termed microsatellite instability (MSI).[7] As the burden of point mutations and MSI increases, genomic stability is lost and cells accumulate malignant properties.[8] The consequences of this cellular dysregulation are most clearly observed in patients with Lynch syndrome who carry germline mutations in one of the MMR proteins.[9] Most commonly, these patients develop colorectal cancer and women who carry these mutations are also at significant risk for endometrial and ovarian cancer.[10] Patients with Lynch syndrome are also at increased risk for gastric, pancreatic, small bowel, urothelial cancers, and gliomas in the brain.[10]

Somatic mutations of MMR proteins and resulting MSI-H status have a significant clinical impact in patients with colorectal cancer. MSI-H status is most prevalent in stage II colon cancer and is considered a good prognostic sign.[11] Compared with colon cancers with low or absent MSI, stage II MSI-H colon cancers have a decreased likelihood of recurrence with surgery alone.[11–14] On the whole, data suggest that adjuvant chemotherapy in MSI-H stage II colon cancer does not improve the already excellent outcomes.[11–13] The excellent outcomes in these patients is thought to be due in part to a more prolific anti-tumor response manifested as higher levels of tumor-infiltrating lymphocytes.[15,16] Infrequently, MSI-H colon cancer evades the endogenous immune response and progresses to metastatic disease.[14] Even in the metastatic setting, the local tumor immune infiltrate has the potential to exert disease control. Analyses of the local tumor microenvironment have shown that MSI-H colon cancers harbor immunosuppressive cells that express a number of inhibitory molecules, including PD-L1.[17] Treatment with one or a combination of check point inhibitors has resulted in significant overall response rates that are durable in patients with metastatic MSI-H colon cancer based on early clinical trial data.[18–20]

In non-colorectal cancers, the influence of MSI-H status on treatment decisions is limited. Encouragingly, patients with metastatic biliary, small bowel, or endometrial cancer with an MMR protein mutation experienced a response to pembrolizumab in a limited phase II clinical trial.[18] Whether MSI status can influence the need for chemotherapy in early-stage disease for the MSI-H non-colorectal cancers will require additional prospective data. ■

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