Chemoradiation improves OS, PFS in older patients with glioblastoma
Patients with MGMT–methylated tumors experienced greatest benefit

Pembrolizumab improves long-term outcomes in advanced melanoma
Patients derived benefit regardless of prior treatment with ipilimumab

Trastuzumab biosimilar safe, effective for advanced breast cancer
Biosimilar has potential as “affordable treatment option” for HER-2–positive breast cancer

Chimeric antigen receptor T cells exhibit efficacy in advanced lymphoma
Anti–CD19 CAR T cells may become “important part of lymphoma therapy”
TARGETING CANCER STEM CELL PATHWAYS AND STEMNESS

Not all cells within a tumor are equal

Despite current advances in cancer therapy, tumor recurrence and metastasis remain a clinical challenge. A potential new approach to address this is targeting a subset of the tumor cell population known as cancer stem cells (CSCs). CSCs are highly tumorigenic, unlike bulk tumor cells. Molecular surface markers for CSCs have been demonstrated within multiple solid and hematologic tumor types, supporting the notion that not all cells within a tumor are equal. This is the basis of the CSC model.1

The CSC model may help explain tumor recurrence

The CSC model is a radical departure from the clonal evolution model. In the clonal evolution model, all cells within a malignant tumor have similar tumorigenic activity. By contrast, in the CSC model only a subset of tumor cells, CSCs, have tumor-initiating capability.2 CSCs are organized in a cellular hierarchy, with the CSCs at their apex having tumor-initiating capability. One important clinical implication of the CSC model is that it may help explain why early tumor shrinkage is often poorly predictive of overall survival.3 While conventional therapies kill the bulk of non-stem cancer cells, resulting in tumor shrinkage, CSCs may remain viable and later reestablish the tumor, leading to relapse.4 Tumors with increased expression of genes associated with CSCs have also been correlated with lower overall survival in breast and lung cancers.5

Stemness of CSCs may lead to tumorigenicity

The heterogeneous high tumorigenicity of CSCs may be a direct result of their stemness. In both normal stem cells and CSCs, stemness is defined by the characteristics of self-renewal and differentiation.6 Unlike normal stem cells, which differentiate into healthy, mature, cell types, CSCs differentiate into cancer cells. The stemness of CSCs is maintained by several signaling pathways that are overexpressed and overactivated, including Wnt/β-catenin, Hedgehog, Nanog, Notch, TGF-β, Hippo-YAP/TAZ, and PI3K/Akt.7,8 These stemness pathways maintain stemness and promote tumorigenicity. This makes CSCs phenotypically different from non-stem cancer cells and confer therapy resistance.9

Epithelial-mesenchymal transition (EMT) of CSCs may lead to metastasis

CSCs are also able to transform to a mesenchymal state by the process of EMT. In this state, CSCs become highly migratory and invasive and therefore prone to metastasis.10,11 After spreading to a distant site, they can undergo mesenchymal-epithelial transition and become tumorigenic, colonizing the new site.12 This is a potential mechanism for how CSCs contribute to metastasis and recurrence. Some evidence suggests that EMT and stemness may be coupled, as they are mediated by many of the same factors.13

CSCs are highly resistant to conventional cancer therapies

Although current chemotherapies and radiotherapy can kill most non-stem cancer cells, CSCs remain highly resistant.14,15 Further, conventional therapies have been shown to increase the percentage of CSCs within malignant residual tumors.16,17 Many mechanisms that mediate the therapy resistance of CSCs have been identified, including overactivated stemness signaling.18

A key implication of the CSC model for cancer treatment is that both CSCs and non-stem cancer cells should be targeted to reduce tumor recurrence and metastasis.19 Several approaches to targeting CSCs are being studied, including stemness-associated signaling pathways that may mediate tumorigenesis, metastasis, and resistance.20 The next generation of cancer therapeutics is in development with investigational agents designed to inhibit stemness pathways.21

References:

The ASCO Annual Meeting, held in Chicago from June 3-7 under the theme "Collective wisdom: The future of patient-centered care and research," brought together hematologists and oncologists from around the world for 5 days of late-breaking clinical trials and research updates. Key areas of focus included breast cancer, glioblastoma and melanoma. Numerous presentations also demonstrated the benefits of immunotherapy in multiple cancer subtypes. An address by Vice President Joe Biden on the national cancer moonshot initiative focused on collaboration and “a lot more openness” among clinicians and researchers.

This HemOnc Today supplement provides readers with an overview of the most noteworthy – and potentially practice-changing – findings presented at the ASCO Annual Meeting. Perspectives from physicians in the hematology/oncology communities provide further insight into the impact these findings may have in everyday practice.

— The Publishers of HemOnc Today

WEB WATCH

Visit Healio.com/Hematology-Oncology to hear more from in-depth coverage of the findings in immuno-oncology presented at the meeting in the Discoveries from ASCO: Immuno-oncology resource center. The resource center provides exclusive video perspectives from key opinion leaders regarding late-breaking clinical trials and other recent research in immuno-oncology to be presented at the ASCO Annual Meeting.

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"Figuring out how to work with pharma to try to moderate … drug pricing is utterly imperative both for the health care economy, as well as for our citizens."

— BRIAN BOLWELL, MD
Chemoradiation improves OS, PFS in older patients with glioblastoma

The addition of concomitant and adjuvant temozolomide to hyperfractionated radiation therapy significantly prolonged PFS and OS among older patients with newly diagnosed glioblastoma, according to phase 3 study results presented during the plenary session of the ASCO Annual Meeting.

Patients with MGMT–methylated tumors derived the greatest benefit from temozolomide. Although glioblastoma occurs primarily in older adults, no clear guidelines for treatment have been defined.

“The peak age of incidence of glioblastoma is 64 years, and the incidence appears to be increasing with our aging population,” James R. Perry, MD, FRCP, Crolla family endowed chair in brain tumor research at Odette Cancer Centre and Sunnybrook Health Sciences Centre in Toronto, said during a press conference. “The current best practice is surgical resection, followed by radiotherapy combined with chemotherapy.”

A trial conducted by the EORTC suggested a survival benefit could be gained through the addition of temozolomide to radiation therapy in newly diagnosed patients; however, the researchers observed a trend of decreasing benefit with increasing age, and the potential OS benefit of the combination in older patients remained unknown.

“The studies that we have in older patients over 65 years have only compared radiation schedules head-to-head, or radiation alone vs. temozolomide alone,” Perry said. “There has never been a trial of combined chemotherapy with radiation in elderly patients.”

Perry and colleagues conducted a global randomized clinical trial of 562 older patients (median age, 73 years; range, 65-90; 61% men). Researchers randomly assigned patients to 40 Gy radiation therapy in 15 fractions, with or without 3 weeks of concomitant temozolomide and monthly adjuvant temozolomide (n = 281 for both). Patients assigned adjuvant temozolomide received treatment for up to 12 cycles or until progression.

Patients assigned temozolomide achieved longer median OS (9.3 months vs. 7.6 months; HR = 0.67; 99% CI, 0.56-0.8) and longer median PFS (5.3 months vs. 3.9 months; HR = 0.5; 95% CI, 0.41 (0.6) than those assigned radiation alone. A total of 462 patients provided an adequate tissue sample for MGMT analysis, which has been conducted in 354 patients to date.

Chemoradiation continues on page 7

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The take-home message of this trial is that, regardless of the age of the adult patient, it is now becoming the standard of care to give radiotherapy plus temozolomide to patients with newly diagnosed glioblastoma. The second important takeaway is that the benefit of temozolomide was most pronounced among those with glioblastomas that demonstrated methylation of the promoter for a gene called MGMT. However, there was also a benefit regardless of MGMT methylation.

The context for why this is important is twofold. One, the prior practice-changing trial that led to our current standard of care to give radiotherapy and temozolomide in patients with glioblastoma excluded patients aged older than 70 years. In addition, that prior trial suggested the benefit of temozolomide decreased with age. Therefore, it was unclear whether temozolomide prolonged survival when combined with radiotherapy in patients aged older than 70 years.

The other important aspect of this study was the length of the radiotherapy course. In this trial it was 3 weeks, whereas it was 6 weeks in the prior landmark trial by Stupp and colleagues. Six weeks of radiotherapy can be a rough treatment in older patients, and there had been previous studies demonstrating that a shortened course, using a technique called hypofractionation, was not inferior to a 6-week course in older patients.

What remains unclear is whether radiotherapy itself can be omitted in elderly patients with MGMT–methylated tumors. This trial included two arms, both of which had radiation. The question was whether adding temozolomide to radiation was beneficial, and the answer was yes. The flip question of randomly assigning patients to get temozolomide alone or with radiotherapy remains unanswered.

References:

— Andrew B. Lassman, MD
NewYork-Presbyterian
Columbia University Medical Center
Disclosure: Lassman reports no relevant financial disclosures.

Age, complications influence death after colon cancer surgery

Postoperative complications increased the 1-year risk for death after colon cancer surgery among patients of all ages, according to study results presented during the 30-day postoperative period, and nearly one-quarter of patients aged older than 65 years died of cardiovascular disease.

A trial conducted by the EORTC fractionated radiation therapy significantly prolonged OS and PFS among older patients (median age, 73 years; range, 65-90; 61% men).

For patients assigned radiation alone, HR was 0.67 (99% CI, 0.56-0.8). For those assigned a combination of chemotherapy and radiotherapy, HR was 0.5 (95% CI, 0.41 (0.6) than those assigned radiation alone. A total of 462 patients provided an adequate tissue sample for MGMT analysis, which has been conducted in 354 patients.

Chemoradiation analysis, which has been conducted in 354 patients to date.

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PERSPECTIVE

Daneng Li
City of Hope
Disclosure: Li reports no relevant financial disclosures.

“Traditionally, there has not been as much focus placed on the management of the patient’s other comorbidities, which may be driving the higher rates of death from cardiovascular disease.”

— CHRISTOPHER THOMAS AGUINA, MD, MPH

Few studies have focused on age-related differences in the rate and cause of deaths beyond the postoperative period among patients undergoing colorectal surgery. Most of the previous studies looking at long-term outcomes have focused on oncologic endpoints, such as RFS, to analyze the effects of different treatment regimens, Christopher Thomas Aguina, MD, MPH, surgical resident at University of Rochester Medical Center and research fellow at Surgical Health Outcomes & Research Enterprise, told HemOnc Today.

“This research has been critical in improving outcomes for patients, but it has not traditionally accounted for other factors influencing OS.”

Aguina and colleagues accessed the New York State Cancer Registry and Statewide Planning and Research Cooperative System to identify 26,420 patients who underwent colectomy for stage I to stage III colon adenocarcinoma between 2004 and 2011.

The researchers categorized patients by age group — younger than 65 years, 65 years to 74 years, and 75 years or older — and by occurrence of major complications. They then compared age groups with cause of death 1 year after surgery.

Overall, 3.3% of patients died within 30 days of surgery, and 11.6% died within 1 year. Mortality varied by age group (< 65 years, 3.8%; 65-74 years, 8.3%; ≥ 75 years, 18.8%). A greater percentage of older patients expressed a major complication (< 65 years, 23.3%; 65-74 years, 29.9%; ≥ 75 years, 38.2%).

Postoperative complications significantly increased the risk for death at 1 year across all age groups: aged older than 65 years (6.4% vs. 1.9%); 65 to 74 years (12.8% vs. 3.8%); 75 years or older (22.4% vs. 9.2%; P < .001 for all).

Although colon cancer was the leading cause of death in all cohorts, a greater proportion of younger patients died of the disease than older patients (< 65 years, 58%; ≥ 75 years, 43.9%). However, the risk for death caused by cardiovascular disease increased with age. More than one-quarter (27.8%; n = 429) of patients aged 75 years or older died of cardiovascular disease, compared with 9.3% (n = 21) of patients aged younger than 65 years and 20.7% (n = 83) of patients aged 65 years to 74 years.

“The major focus following surgery typically involves preventing cancer recurrence through close oncologic follow-up,” Aguina said. “However, the risk for death caused by cardiovascular disease increased with age. More than one-quarter (27.8%; n = 429) of patients aged 75 years or older died of cardiovascular disease, compared with 9.3% (n = 21) of patients aged younger than 65 years and 20.7% (n = 83) of patients aged 65 years to 74 years.”

“A greater percentage of older patients expressed a major complication (< 65 years, 23.3%; 65-74 years, 29.9%; ≥ 75 years, 38.2%). Postoperative complications significantly increased the risk for death at 1 year across all age groups: aged older than 65 years (6.4% vs. 1.9%); 65 to 74 years (12.8% vs. 3.8%); 75 years or older (22.4% vs. 9.2%; P < .001 for all).

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This study adds to the landscape of knowledge in terms of postoperative outcomes in older adults who undergo surgery for colon cancer. This study highlights the importance of integrating geriatric oncology practices. As patients aged, the overall risk for postoperative complications increased, resulting in higher rates of 1-year mortality.

Two individuals with the same chronological age do not necessarily have the same functional or physiological age. The study of the use of geriatric oncology principles, such as a comprehensive geriatric assessment, is already underway in terms of preoperative assessment for older adults getting ready for surgery. This is important because doctors can identify potential vulnerabilities that a surgeon might not be able to anticipate through a standard history or physical exam. As a result of that, we can research potential interventions for vulnerabilities detected through the geriatric assessment to improve overall surgical outcomes.

This study identifies age as a risk factor for long-term mortality, and it really emphasizes the need for geriatric oncology principles and comprehensive geriatric assessment in the preoperative and perioperative settings.

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This study identifies age as a risk factor for long-term mortality, and it really emphasizes the need for geriatric oncology principles and comprehensive geriatric assessment in the preoperative and perioperative settings.
Chimeric antigen receptor T cells exhibit efficacy in advanced lymphoma

T

treatment with T cells genetically modified to express chimeric anti-
genetic receptors that target CD19

induced remission in patients with advanced B-cell lymphoma when ad-

ministered with low-dose chemotherapy.

The use of chimeric antigen receptor (CAR) T cells may become

a standard of care for advanced lymphoma in the near future, according to

James N. Kochenderfer, MD, investigat-
in the experimental transplantation

and immunology branch of the NCI’s Center for Cancer Re-

search.

"T cells that are genetically modi-

fied to express CARs targeting CD19

have significant activity against B-cell

malignancies," Kochenderfer said
during his presentation. "In almost

all cases, CAR T cells had a CR rate of

68% in the DLBCL patient population.

Eight patients with DLBCL achieved complete response, as did

all patients with follicular lymphoma and mantle cell lymphoma.

Five patients with DLBCL achieved a partial response, with two patients

achieving stable disease. Four patients

experienced progressive disease.

Ten patients’ responses remained

ongoing at the time of reporting, with

response durations ranging from 1

month to 20 months.

All but four patients had chemo-

therapy-refractory lymphoma or re-
lapsed lymphoma after autologous stem cell transplantation.

All patients developed fevers, and

55% (n = 12) experienced grade 3 or

greater in toxicity from CAR T cells.

In most of these cases, the

toxicities resolved, typically

in less than 2 weeks, Kochenderfer
described.

Patients had a median CAR-positi-
tive cell level of 47% (range, 4%-117%).

Those who achieved complete or par-
tial responses had higher peak blood

CAR-positive cell levels than those

with stable or progressive disease.

“Anti-CD19 CAR T cells are now

involved in multicenter trials,” Kochen-
derfer said. “They will proba-
bly become an important part of

lymphoma therapy in the future,

particularly to salvage the patients

who are refractory to chemotherapy

and have very few other options.”

— by Cameron Kelsall

Reference:


at: ASCO Annual Meeting; June 3-7, 2016,

Chicago.

Disclosure: The NIH funded this study.

Kochenderfer reports institutional research fund-
ing from Bluebird Bio and Kite Pharma, as well

as a patient agreement with Bluebird Bio. Please

see the abstract for a list of all other researchers’

relevant financial disclosures.

Chimeric antigen receptor T cells exhibit efficacy in advanced lymphoma

asi, Kochenderfer and colleagues

previously reported data from patients

treated with CAR T cells and high-
dose chemotherapy.

In the current analysis, researchers

assigned 22 patients with advanced lymphoma to low-dose condition-
ing chemotherapy, followed by anti-

CD19 CAR T-cell infusion.

Nineteen patients had diffuse large B-cell lymphoma (DLBCL). Two pa-
included, but most of the patients

in this report had DLBCL. A majority of patients in this study had a response. This

is exciting because it shows we can observe a high response rate when patients are

with CAR T cells. Further, the chemotherapy regimen used was attenuated

dose, so we can attribute the effect primarily to the CAR T cells and less so to the

chemotherapy.

These additional data show this regimen has potential in the treatment of patients

with resistant, aggressive lymphoma. As far as follow-up is concerned, we need

additional studies with larger groups of patients, with longer follow-up periods, to

see if these responses are going to be durable. That is going to be quite important

to see in much larger patient populations. We also need to address the critical fact

that there is an inherent selection bias in CAR T-cell therapy. There are patients

who are not candidates for this type of treatment because of their age and comorbidities

or burden, or because they have rapidly aggressive or growing disease. Because there

is an inherent delay of a few weeks required to get a patient enrolled and get them

CAR T cells — and sometimes longer to even be able to be considered for a spot on

a trial — some patients with aggressive lymphoma are left out because they

cannot wait that long for therapy. So, there is an inherent bias toward patients who

are healthy, and those who have more favorable (ie, less rapidly growing or symp-
tomatic) disease, allowing them to wait a little longer for treatment.

That said, the lymphoma community remains excited, and it is safe to say there is a

good chance this treatment will be more widely used in the future.

— John P. Leonard, MD

Weill Cornell Medicine

NewYork-Presbyterian Hospital

Disclosure: Leonard reports a prior consultant role with Kite Pharma.

Chemoradiation

continued from page 4

Among the 165 patients with

Mycanmethylated tumors, those as-
tended temozolomide achieved higher median OS than those assigned radia-
tion alone (13.5 months vs. 7.7 months; HR = 0.53; 95% CI, 0.38-0.73).

Unmethylated patients assigned

the combination had a median OS of

10 months, compared with 7.9 months

for those assigned radiation (HR = 0.75; 95% CI, 0.56-1.01).

A quality-of-life analysis showed no differences in physical, cognitive, emo-
tional or social functioning between

arms. Patients assigned temozolomide

reported more nausea, vomiting and constipation than those assigned ra-
diation alone.

The researchers reported high pa-
tient adherence to therapy, with more

than 97% of patients completing 3

weeks of chemoradiation.

“That is quite important, because the elderly often have difficulties with

mobility, or with distance from treat-

ment centers,” Perry said. “They some-
times don’t have a caregiver who is able to bring them back and forth to treat-

ment, so the shorter radiation schedule is an advantage.”

Thirty-nine percent of patients as-
tended temozolomide, and 41% of

patients assigned radiation alone re-

ceived systemic therapy after progres-
sion.

“Oncologists now have evidence to consider radiotherapy with temozolo-

dazole in all newly diagnosed elderly patients with glioblastoma,” Perry said.

— by Cameron Kelsall

Reference:


at: ASCO Annual Meeting; June 3-7, 2016,

Chicago.

Disclosure: This study received funding from the

Canadian Cancer Society Research Insti-
tute, as well as from an unrestricted grant from

Schering Plough/Merck. Perry reports stock

and ownership interests in DelMar Pharma-

ceuticals and VBL Therapeutics. Please see

the abstract for a list of all other researchers’

relevant financial disclosures.

Age

continued from page 5

ologic follow-up and appropriate use

of chemotherapy,” Aquina said. “Tra-

ditionally, there has not been as much

focus placed on the management of the patient’s other comorbidities,

which may be driving the higher rates of death from cardiovascular disease.

Older patients are more likely to have higher rates of cardiovascular disease and a higher overall level of comor-

bidity burden compared with younger

patients.”

Aquila told HemOnc: Today that he

hopes these data will lead to stron-
ger collaborations between surgeons and medical oncologists.

“We hope that this work empha-
sizes the need for greater collabora-
tion with our colleagues in geriatric oncology to allow for a more nuanced

prospective assessment, including a comprehensive geriatric assessment

when appropriate,” Aquina said. “We

feel that multidisciplinary support will help improve the delivery of care to

older patients with colon cancer.”

— by Cameron Kelsall

Reference:


at: ASCO Annual Meeting; June 3-7, 2016,

Chicago.

Disclosure: Aquina reports no relevant fi-
nancial disclosures. Other researchers report

consultant roles with Seattle Genetics and

UpToDate.
Not all cells within a tumor are equal

Despite current advances in cancer therapy, tumor recurrence and metastasis remain a clinical challenge. A potential new approach to address this is the targeting of a subset of the tumor cell population known as cancer stem cells (CSCs). CSCs are highly tumorigenic, unlike bulk tumor cells. Molecular surface markers for CSCs have been demonstrated within multiple solid and hematologic tumor types, supporting the notion that not all cells within a tumor are equal. This is the basis of the CSC model.

The CSC model may help explain tumor recurrence

The CSC model is a radical departure from the clonal evolution model. In the clonal evolution model, all cells within a malignant tumor have similar tumorigenic activity. By contrast, in the CSC model only a subset of tumor cells, CSCs, have tumor-initiating capability. CSCs are organized in a cellular hierarchy, with the CSCs at their apex having tumor-initiating capability. One important clinical implication of the CSC model is that it may help to explain why early tumor shrinkage is often poorly predictive of overall survival. While conventional therapies kill the bulk of non-stem cancer cells, resulting in tumor shrinkage, CSCs may remain viable and later reestablish the tumor, leading to relapse. Tumors with increased expression of genes associated with CSCs have also been correlated with lower overall survival in breast and lung cancers.

Stemness of CSCs may lead to tumorigenicity

The heterogeneous high tumorigenicity of CSCs may be a direct result of their stemness. In both normal stem cells and CSCs, stemness is defined by the characteristics of self-renewal and differentiation. Unlike normal stem cells, which differentiate into healthy, mature, cell types, CSCs differentiate into cancer cells. The stemness of CSCs is maintained by several signaling pathways that are overexpressed and overactivated, including JAK-STAT, Wnt/β-catenin, Hedgehog, Nanog, Notch, TGF-β, Hippo-YAP/TAZ, and PI3K/Akt. These stemness pathways maintain stemness and promote tumorigenicity. This makes CSCs phenotypically different from non-stem cancer cells and confers therapy resistance.

Epithelial-mesenchymal transition (EMT) of CSCs may lead to metastasis

CSCs are also able to transform to a mesenchymal state by the process of EMT. In this state, CSCs become highly migratory and invasive and therefore prone to metastasis. After spreading to a distant site, they can undergo mesenchymal-epithelial transition and become tumorigenic, colonizing the new site. This is a potential mechanism for how CSCs contribute to metastasis and recurrence. Some evidence suggests that EMT and stemness may be coupled, as they are mediated by many of the same factors.

CSCs are highly resistant to conventional cancer therapies

Although current chemotherapies and radiotherapy can kill most non-stem cancer cells, CSCs remain highly resistant. Further, conventional therapies have been shown to increase the percentage of CSCs within malignant residual tumors. Many mechanisms that mediate the therapy resistance of CSCs have been identified, including overactivated stemness signaling.

A key implication of the CSC model for cancer treatment is that both CSCs and non-stem cancer cells should be targeted to reduce tumor recurrence and metastasis. Several approaches to targeting CSCs are being studied, including stemness-associated signaling pathways that may mediate tumorigenesis, metastasis, and resistance. The next generation of cancer therapeutics is in development with investigational agents designed to inhibit stemness pathways.

Learn more at www.bostonbiomedical.com

Boston Biomedical is developing the next generation of cancer therapeutics with drugs designed to inhibit cancer stemness pathways. Clinical trials are underway with the goal of reducing recurrence and metastasis.
FORTY percent of patients with advanced melanoma achieved 3-year OS with pembrolizumab, according to a long-term follow-up of the KEYNOTE-001 study. Patients derived benefit from pembrolizumab (Keytruda, Merck) regardless of prior treatment with ipilimumab (Yervoy, Bristol-Myers Squibb).

“The data show durable responses in one-third of patients, with complete durable responses that are visible after stopping treatment,” Pembrolizumab received accelerated approval for advanced melanoma in September 2014 based on data from KEYNOTE-001. Data from KEYNOTE-002 also has shown that pembrolizumab prolongs PFS compared with chemotherapy, and in KEYNOTE-006, pembrolizumab extended OS and PFS compared with ipilimumab for patients with advanced melanoma. Prior to the approval of ipilimumab in 2011, median survival for advanced melanoma had been less than 1 year, Robert said.

Robert and colleagues conducted long-term follow-up of patients treated in the KEYNOTE-001 study to determine 3-year OS. The analysis included 655 patients — enrolled into ipilimumab-naive and -treated cohorts — assigned 2-mg/kg or 10-mg/kg doses of pembrolizumab every 3 weeks or 10 mg/kg every 2 weeks until intolerable toxicity, disease progression or investigator decision to stop treatment. Seventy-five percent of patients had received one or more previous therapies and 52% had received ipilimumab.

Following pembrolizumab discontinuation, researchers followed up patients every 3 months to assess OS. Median follow-up was 32 months (range, 24-46); all patients were followed for a minimum of 2 years. Mean treatment duration was 11.3 months and 21% of patients continued pembrolizumab beyond the data cutoff date of Sept. 18, 2015. Overall, 358 patients died. The 3-year OS rate was 40% and median OS was 23.8 months (95% CI, 20.2-29). OS rates appeared similar across treatment regimens, with the highest median OS being 2 months (95% CI, 18.9-41.8) in the cohort that received 10 mg/kg every 2 weeks. The rate of 3-year OS was 41% both in cohorts who had and had not previously received ipilimumab. However, 3-year OS was higher in treatment-naive patients (45%), for whom median OS was 32 months (95% CI, 27.1- not reached).

Ninety-five patients achieved a complete response, 61 of whom stopped treatment as a result. Response duration ranged from 17+ months to 43+ months. Two patients experienced disease progression after stopping treatment, Pembrolizumab continues on page 13

Pembrolizumab improves long-term outcomes in advanced melanoma

This abstract reports on long-term survival outcomes in patients with advanced melanoma treated with pembrolizumab (Keytruda, Merck) in the KEYNOTE-001 trial. Researchers report a 40% 3-year OS rate with a median survival of nearly 2 years and a “tail-of-the-curve” phenomenon consistent with long-term survival benefit with this agent.

These data mirror the long-term outcomes with nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda, Merck) in the KEYNOTE-001 trial. Researchers previously demonstrated a 42% 3-year OS rate and a 34% 5-year OS rate. For more than 2 decades, chemotherapeutic agents were the mainstay of treatment for advanced melanoma, “For more than 20 years, the role of upfront autologous HSCT superior to novel therapies for multiple myeloma.” Michele Cavo, MD, head of the Surgical Institute of Hematology at University of Bologna, said during a press briefing. “Over the past 10 to 15 years, therapies with novel, nongenotoxic drugs have dramatically increased the response rate and significantly [extended] survival in previously untreated myeloma patients. Remarkable activity of novel therapies has recently put into question the role of upfront autologous stem cell transplantation in multiple myeloma.

Cavo and colleagues compared the efficacy of the VMP chemotherapy regimen — which consists of bortezomib (Velcade; Takeda/Millennium), melphalan and prednisone — with autologous HSCT in 1,266 patients aged 65 years or younger with newly diagnosed multiple myeloma. All patients received induction therapy with bortezomib, cyclophosphamide and dexamethasone. They then were randomly assigned to four cycles of VMP (n = 512) or one to two courses of high-dose melphalan with single autologous HSCT (n = 754).

Patients treated in centers with a tandem HSCT policy were randomly assigned to receive VMP or single or double autologous HSCT. PERSPECTIVE

Upfront autologous HSCT superior to novel therapies for multiple myeloma

With the arrival of noncytotoxic agents in the early 2000s, the role and timing of high-dose melphalan was evaluated in several randomized phase 3 studies. Palumbo and colleagues with the European Myeloma Network conducted two randomized phase 3 trials evaluating lenalidomide (Revlimid, Celgene) and low-dose dexamethasone induction followed by conventional chemotherapy — melphalan, prednisone and lenalidomide in one trial, and cyclophosphamide, prednisone and lenalidomide in the other — or high-dose melphalan with autologous stem cell transplantation (HDASCT, single or tandem). Both trials showed PFS and OS benefits with HD-ASCT but were criticized for not having proteasome inhibitors in induction treatment.

Attila and colleagues then presented the Intergroupe Francophone du Myelome IFM2009 data — which compared early vs. late HD-ASCT — at the ASH Annual Meeting and Exposition in 2015. Results showed a PFS benefit in favor of early HD-ASCT. All patients on the IFM 2009 trial received lenalidomide, bortezomib (Velcade, Takeda/Millennium) and dexamethasone induction and lenalidomide maintenance, thus quelling concerns about suboptimal induction. Now, Cavo and colleagues have presented another clinical trial in which bortezomib, cyclophosphamide and dexamethasone induction was followed by either bortezomib, melphalan and prednisone consolidation or HD-ASCT (single or tandem).

Data from the study follow the same theme: HD-ASCT conferred superior PFS. The PFS benefit was seen in patients with standard- and high-risk cytogenetics and was more pronounced in the tandem HD-ASCT arm. If we are compelled to use best available evidence and data to treat our patients, then upfront/early HD-ASCT should remain the standard of care for transplant-eligible patients with multiple myeloma.

PERSPECTIVE

Saad Z. Usmani

References:

— Saad Z, Usmani, MD, FACP

Hematology—Oncology, Editor, and Board member

Levine Cancer Institute, Carolinas HealthCare System Disclosures: Usmani reports no relevant financial disclosures.

Disclosure: Usmani reports no relevant financial disclosures.
Trastuzumab biosimilar safe, effective for advanced breast cancer

Women with HER-2–positive advanced breast cancer treated with MYL-1401O, a biosimilar trastuzumab antibody, achieved outcomes comparable to those of women treated with the biosimilar’s FDA-ap proved reference product, according to results of a randomized phase 3 study.

The addition of trastuzumab (Herceptin, Genentech) — a biologic agent approved by the FDA in 1998 — is a treatment option for women with early- or late-stage breast cancer — to chemotherapy has resulted in a 5- to 8-month survival improvement for women with late-stage disease. The addition of 1 year of trastuzumab to chemotherapy has been shown to reduce the risk for recurrence by 10% and improve survival by about 9% in women with early-stage disease. “Biologic agents are usually targeted across the globe,” Hope S. Rugo, MD, professor of medicine at University of California, San Francisco, said during a press conference. “Many biologic agents are losing patent protection soon or have already lost patent protection in other countries. Biosimilars have the potential to significantly improve access to expensive agents.”

Rugo and colleagues evaluated the safety, efficacy and immunogenicity of MYL-1401O (Mylan Inc.) compared with trastuzumab. The analysis included data from 458 women treated at 95 sites worldwide. All women had HER-2–positive metastatic breast cancer, and they had not received prior chemotherapy or trastuzumab for metastatic disease. Forty-four percent of women had hormone receptor–positive disease.

Researchers randomly assigned patients to MYL-1401O (n = 230) or trastuzumab (n = 228) with docetaxel or paclitaxel every 3 weeks for at least eight cycles. Patients with stable disease beyond the eighth cycle could continue to receive the antibody therapy alone until disease progression or unacceptable toxicity.

Overall response rate at week 24 served as the study’s primary endpoint. The FDA also asked researchers to calculate ORR ratio as an endpoint, and the European Medicines Agency asked for the difference in ORR between the biosimilar and trastuzumab. Secondary endpoints included PFS, OS and safety.

At week 24, the ORR was 69.6% for MYL-1401O and 64% for trastuzumab. Researchers calculated an ORR ratio of 1.09 (90% CI, 0.97-1.21; and 95% CI, 0.95-1.23), meeting the predefined equivalence margin. The difference in ORR was 5.5 (90% CI, 1.7-12.69; and 95% CI, 3.08-14.04), which also fell within the required equivalence range.

Based on 41 events in the biosimilar arm and 48 in the reference product arm, median PFS had not yet been reached.

The overall antitumor antibody rate was 2.4% with MYL-1401O and 2.8% with trastuzumab, consistent with published data, Rugo said. The dose-normalized maximum concentration and area under the curve also were similar between the two agents.

Safety appeared comparable between study groups, and no significant changes in cardiac function occurred in either cohort. Serious adverse events — which were primarily hematologic and related to taxane therapy — occurred in 38.1% of those assigned the biosimilar and 36.2% of those assigned the reference product.

Common adverse events included neutropenia (biosimilar, 27.5%; reference product, 25.2%), febrile neutropenia (4.5% vs. 4.1%), leucopenia (1.6% vs. 4.9%) and pneumonia (1.6% vs. 2%).

Four fatal events occurred in each study arm.

“This proposed biosimilar has the potential to meet the need for an affordable treatment option for patients with HER-2–positive cancers,” Rugo said. “This is one of the first trials of biosimilars in oncology to demonstrate these similar results. Ongoing trials with other biosimilars should further improve access worldwide to these lifesaving therapies.” — by Alexandra Todak

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one of whom restarted treatment with pembrolizumab.

The safety profile of pembrolizumab appeared comparable to data from other studies. The most common adverse events included fatigue (40%), itchiness (28%) and rash (23%). Eight percent of patients discontinued treatment due to adverse events.

“Advanced melanoma is still a very challenging cancer, which is why it is so remarkable that such a large proportion of patients see a long-term survival benefit from this therapy,” Robert said in a press release. “The results of this study further demonstrate the potential for long-term benefit with pembrolizumab.” — by Nick Andrews

Reference:

Disclosure: The study was funded by Merck.

Reference:

Disclosure: The FDA also asked researchers to calculate ORR ratio as an endpoint, and the European Medicines Agency asked for the difference in ORR between the biosimilar and trastuzumab.
Off-label therapies benefit patients with advanced, mutated cancers

Patients with nine different tumor types benefited from targeted therapies administered outside of current drug indications, according to the results of a basket study presented at the ASCO Annual Meeting. The researchers intend to expand cohorts of patients with HER-2–amplified colorectal cancer, bladder cancer and biliary cancer, as well as BRAF–mutated lung cancer, based on the observed outcomes.

“This increasing number of targeted agents for advanced cancer are approved now based on the presence of molecular abnormalities in the cancers,” John D. Hainsworth, MD, senior investigator at Sarah Cannon Research Institute in Nashville, Tennessee, said during a press conference. “Major successes in this area include HER-2–targeted treatment for HER-2–positive breast cancer and BRAF–targeted treatment for melanoma. We have known, though, that the same mutations are found in a wide variety of other cancers, although at a lower incidence. It is difficult to test how efficient these same treatments are, due to the difficulty of identifying the patient population.”

The MyPathway study included data from 129 patients with advanced solid tumors and no available curative therapy. Patients’ tumors harbored the following alterations:

- HER-2 amplification (n = 53), mutation (n = 23), both (n = 5) or RBMS-NRG1 fusion (n = 1)
- BRAF V600E (n = 18) or other (n = 15)
- Hedgehog (Hh) PTCH1 (n = 7) or SMO (n = 1); or
- EGFR (n = 6)

Patients enrolled in the trial had received a median of three (range, 0-10) prior lines of therapy. The researchers evaluated the use of therapies targeting these alterations, including trastuzumab (Herceptin, Genentech) and pertuzumab (Perjeta, Genentech) for patients with HER-2 amplification; vemurafenib (Zelboraf, Genentech) for patients with BRAF alterations; vismodegib (Erivedge, Genentech) for patients with Hh alterations; and erlotinib (Tarceva; Genentech, Astellas) for patients with EGFR mutations.

Investigator-assessed response rate within the tumor-pathway cohort served as the study’s primary endpoint. Eleven patients had insufficient follow-up data and were not included in the analysis. Twenty-nine patients achieved a partial response or complete response, including one complete response achieved by a patient with HER-2–amplified colorectal cancer.

Researchers also observed responses in three patients with HER-2–amplified bladder cancer and three with HER-2–amplified biliary cancer (lung cancer, n = 2; salivary gland cancer, n = 1); three patients with BRAF–mutated lung cancer; one case each of BRAF–mutated ovarian cancer, cancer of unknown primary origin, colon cancer, pancreatic cancer, and head and neck cancer; and two patients with Hh alterations (squamous cell carcinoma, n = 1; cancer of unknown primary origin, n = 1).

Three patients with BRAF–mutated lung cancer achieved objective responses, and two achieved stable disease. The researchers will expand this cohort based on these data. Responses continued up to 11 months. Fourteen responding patients progressed, at a median of 6 months.

“This trial design is feasible, with patients selected based on molecular abnormalities in their cancers rather than on their primary tumor type or primary site.” — JOHN D. HAINSWORTH, MD

Researcher, and corporate new agents that target additional molecular alterations. “It offers opportunities for patients with these molecular abnormalities.” — by Cameron Kelsall

Researcher

“The MyPathway study is both a basket trial and an umbrella trial. Basket trials look at genomic alterations across different histologies. For instance, in this study, if you have a BRAF mutation, it does not matter if you have breast, lung or colorectal cancer — it all goes in the basket. Yet, it also is an umbrella trial, because it includes four different baskets. We are, therefore, getting a lot of mileage out of this one trial.”

It is much more efficient to have one trial with four different baskets rather than having four basket trials. The most interesting part of this trial is the HER-2 basket. Patients with a variety of different tumor types — including colorectal cancers and biliary tumors — are having really nice responses, and this is going to be very important. It is remarkable that we are seeing responses in diseases like colorectal cancer from giving a drug that would usually be given to patients with breast cancer or gastric cancer.

In the future, we will see more basket trials, because they make a lot of sense. However, organizations and institutions will need to have a system in place to be able to do them. It would be really difficult to perform a genomically based basket trial if genomic sequencing is not part of the practice, because these alterations are rare, and only very small subsets will have the alterations. For colorectal cancer, it may only be 2% or 3% that have HER-2 alterations. If you are not regularly checking for it, you are not going to be able to accrue patients. It is really difficult to have to put 100 patients on a trial in order to find one who is eligible, so you have to be doing sequencing regularly.

Further, a lot of academic centers that do clinical trials are very siloed. Colorectal cancer researchers do not work together with the head and neck cancer researchers. They are all in their own territories. For a trial like this, you have to have a system that allows you to work across diseases. These barriers will not be hard to overcome, but I do not know that all centers are ready to work with a trial like this one.

— RAZELLE KURZROCK, MD

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Disclosure: Kurzrock reports research funding from Foundation Medicine.

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PFS from the time of the first randomization to the study’s primary endpoint.

Cavo presented data from an interim analysis performed in January after 33% of required events had occurred. Median follow-up time from the first randomization was 23.9 months.

Although median PFS had not yet been reached, patients assigned high-dose melphalan and autologous HSCT were less likely than those assigned VMP to experience disease progression (HR = 0.76; 95% CI, 0.61-0.94).

This benefit persisted across patient subgroups, including among patients with revised International Staging System stage III disease (HR = 0.52; 95% CI, 0.32-0.84) and high-risk cytogenetics (HR = 0.72; 95% CI, 0.54-0.97).

A greater proportion of patients assigned transplant achieved at least a very good partial response (84% vs. 74%; OR = 1.9; 95% CI, 1.42-2.54).

Cox regression analysis results showed randomization to the transplantation arm independently predicted longer PFS (HR = 0.61; 95% CI, 0.45-0.82).

“These preliminary results do support the conclusion that upfront high-dose chemotherapy and autologous transplant continues to be the best treatment option for fit patients with newly diagnosed myeloma, even in the novel-agent era,” Cavo said.

— by Alexandra Todak

Reference:

Disclosure: The study was funded by the Haemato Oncology Foundation for Adults in the Netherlands. Cavo reports honoraria and travel expenses from and consultant/advisory roles with Amgen, Bristol-Myers Squibb, Celgene, Genentech, Johnson & Johnson, Eli Lilly and Novartis. Please see the abstract for a list of all other researchers’ relevant financial disclosures.
TARGETING CANCER STEM CELL PATHWAYS AND STEMNESS

Not all cells within a tumor are equal

Despite current advances in cancer therapy, tumor recurrence and metastasis remain a clinical challenge.1 A potential new approach to address this is the targeting of a subset of the tumor cell population known as cancer stem cells (CSCs). CSCs are highly tumorigenic, unlike bulk tumor cells.2 Molecular surface markers for CSCs have been demonstrated within multiple solid and hematologic tumor types, supporting the notion that not all cells within a tumor are equal.3,4 This is the basis of the CSC model.2

The CSC model may help explain tumor recurrence

The CSC model is a radical departure from the clonal evolution model. In the clonal evolution model, all cells within a malignant tumor have similar tumorigenic activity.3 By contrast, in the CSC model only a subset of tumor cells, CSCs, have tumor-initiating capability.2 Cancers are organized in a cellular hierarchy, with the CSCs at their apex having tumor-initiating capability.3 One important clinical implication of the CSC model is that it may help to explain why early tumor shrinkage is often poorly predictive of overall survival.4,5 While conventional therapies kill the bulk of non-stem cancer cells, resulting in tumor shrinkage, CSCs may remain viable and later reestablish the tumor, leading to relapse.6 Tumors with increased expression of genes associated with CSCs have also been correlated with lower overall survival in breast and lung cancers.9

Stemness of CSCs may lead to tumorigenicity

The heterogeneous high tumorigenicity of CSCs may be a direct result of their stemness. In both normal stem cells and CSCs, stemness is defined by the characteristics of self-renewal and differentiation.6 Unlike normal stem cells, which differentiate into healthy, mature, cell types, CSCs differentiate into cancer cells. The stemness of CSCs is maintained by several signaling pathways that are overexpressed and overactivated, including JAK-STAT, Wnt/b-catenin, Hedgehog, Nanog, Notch, TGF-β, Hippo-YAP/TAZ, and PI3K/Akt.10-14 These stemness pathways maintain stemness and promote tumorigenicity. This makes CSCs phenotypically different from non-stem cancer cells and confers therapy resistance.4

Epithelial-mesenchymal transition (EMT) of CSCs may lead to metastasis

CSCs are also able to transform to a mesenchymal state by the process of EMT. In this state, CSCs become highly migratory and invasive and therefore prone to metastasize.13,15 After spreading to a distant site, they can undergo mesenchymal-epithelial transition and become tumorigenic, colonizing the new site.15 This is a potential mechanism for how CSCs contribute to metastasis and recurrence. Some evidence suggests that EMT and stemness may be coupled, as they are mediated by the same factors.16

CSCs are highly resistant to conventional cancer therapies

Although current chemotherapies and radiotherapy can kill most non-stem cancer cells, CSCs remain highly resistant.17,18 Further, conventional therapies have been shown to increase the percentage of CSCs within malignant residual tumors.19,20 Many mechanisms that mediate the therapy resistance of CSCs have been identified, including overactivated stemness signaling.10

A key implication of the CSC model for cancer treatment is that both CSCs and non-stem cancer cells should be targeted to reduce tumor recurrence and metastasis.19,21 Several approaches to targeting CSCs are being studied, including stemness-associated signaling pathways that may mediate tumorigenesis, metastasis, and resistance.12 The next generation of cancer therapeutics is in development with investigational agents designed to inhibit stemness pathways.4