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2011 Top Game Changers in Oncology

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Counting Down: Game Changers 10 Through 6

In 2011, great progress was made in the science and management of a variety of cancers. Our Medscape commentators selected and ranked the top 10 game changers in oncology for 2011. Here are their selections.

10. New Regimen Improves Outcomes in Neuroblastoma

A provocative European study[1] showed improved outcomes in high-risk neuroblastoma using a high-dose myeloablative regimen. Until now, the best outcome in neuroblastoma has hovered around the 50% survival threshold, but the new regimen tested has pushed this up to 60%. European investigators say this regimen should be the new standard of care. "This is an incredible success and a great achievement for pediatric oncology," said Julie Park, MD, from Seattle Children's Hospital in Washington, who acted as discussant for the study.

The results are important for patients with this extremely difficult-to-treat disease," said principal investigator Ruth Ladenstein, MD, MBA, Associate Professor of Pediatrics at the University of Vienna, Austria.

Treatment for neuroblastoma comprises several steps. It begins with intense upfront chemotherapy to induce remission (induction) and is followed by surgery and radiation, myeloablative therapy with stem cell transplantation, and then consolidation therapy with 13-*cis*-retinoic acid and immunotherapy, if available.

The European trial used an induction regimen known as rapid COJEC, which consists of both cisplatin and carboplatin, and then compared a high-dose myeloablative regimen known as BuMel (busulphan plus melphalan) with carboplatin, etoposide, and melphalan (control group).

The BuMel group led to significantly improved survival at 3 years compared with the control group (60% vs 48%). "The superiority was based on a lower relapse rate," noted Dr. Ladenstein.

Read the complete Medscape News article on this trial, which was presented during the plenary sessions of the 2011 American Society for Clinical Oncology (ASCO®) annual meeting.

9. A Shooting Gallery of Targets in Lung Cancer

The treatment of non-small cell lung cancer (NSCLC) is undergoing a revolution driven by a greater understanding of the genetic factors fueling this disease. In personalized therapy, drugs are chosen according to the mutations found in the patient's tumor rather than chemotherapy chosen for the organ where the tumor is located.

Contributing to the growing knowledge of genetic targets is a landmark study by the Lung Cancer Mutation Consortium (LCMC),[2] which involves 14 centers across the United States. The LCMC conducted a prospective study in which lung cancer tissue was assessed using a multiplex assay that identified 10 known driver mutations. In addition to *EGFR* and *ALK*, they are testing for *KRAS*, *HER2*, *BRAF*, *PIK3CA*, *AKTI*, *MEKI*, *NRAS*, and *MET*. Many of these mutations have targeted agents under development or, in the case of *HER2*, have targeted drugs already on the market (trastuzumab and lapatinib, which are used in breast cancer). The results so far show that 54% of the tested tumor samples have single-driver mutations. This information is now being used to select patients for first-line therapy with erlotinib or to place these patients into clinical trials with experimental targeted therapies specifically directed at their tumor mutation.

"Although an individual driver mutation may have a single-digit percentage incidence, when you look at all of the possible mutations that exist in lung cancer, you are likely to find a mutation," said Mark G. Kris, MD, lead author and Chief of Thoracic Oncology at Memorial Sloan-Kettering Cancer Center in New York City, in a Medscape commentary. "Even in individuals who did not have a mutation that would suggest a certain clinical trial, we knew what treatments not to give those patients." This study, Dr. Kris added, "brings us one step closer to our goal of personalized medicine."

View the complete commentary by Mark G. Kris, MD, and read the original Medscape News story on this trial, which was reported at the 2011 ASCO® annual meeting.

8. Strongest Data Ever for ER-Positive Breast Cancer

The combination of everolimus plus exemestane produced "the strongest data ever seen in estrogen receptor [ER] -positive breast cancer," principal investigator José Baselga, MD, from the Massachusetts General Hospital and Harvard Medical School, Boston, told *Medscape Medical News*. The pivotal phase 3 study, known as BOLERO-2,[3] was stopped early because of the benefit observed. Results were unveiled at the 2011 European Multidisciplinary Cancer Congress (EMCC).

"Everolimus is the most important advance in breast cancer since trastuzumab," said Fabrice André, MD, PhD, from the Institut Gustave Roussy, Paris, France, who acted as discussant. "The data are robust and are clinically relevant," he said, adding that "the efficacy is in the range of the most important recent advances in the field of medical oncology."

Everolimus is an mTOR inhibitor that has already been approved in the United States for the treatment of progressive neuroendocrine tumors of pancreatic origin and advanced renal cell carcinoma in certain patients. Exemestane is an aromatase inhibitor that is already widely used as adjuvant therapy for ER-positive breast cancer. Both drugs are taken orally.

Read the complete Medscape News story on this trial.

7. Extended Adjuvant Treatment Improves Survival in GIST

Extended adjuvant treatment with imatinib improves survival in patients with high-risk gastrointestinal stromal tumors (GIST). Imatinib administered for 3 years improved both relapse-free survival and overall survival in patients after surgery, compared with 1 year of adjuvant treatment.[4]

Previous data showed that initiating adjuvant imatinib therapy reduces the risk for GIST recurrence compared with placebo. "But the effect of imatinib on overall survival is not known," said lead author Heikki Joensuu, MD, Professor of Oncology at Helsinki University Central Hospital in Finland, who presented the findings during the plenary session here at the ASCO® 2011 annual meeting.

The 5-year relapse-free survival in patients was higher in those who received 3 years of treatment than in those who received 1 year (65.6% vs 47.9%; hazard ratio [HR], 0.46; $P < .0001$). The 5-year overall survival was also better in patients who received 3 years of therapy (92.0% vs 81.7%; HR. 0.45; $P = .019$).

Kathy Miller, MD, Chair of the scientific program for the 2011 ASCO® annual meeting, said in a Medscape commentary, "There had been a lot of debate in the GIST community that perhaps the drug was so effective in people with metastatic disease that you didn't really need to give adjuvant therapy for a longer time or maybe you didn't need to give it at all. You could just catch up and treat these folks when they recurred, and that was definitely not true. A longer duration of therapy, 3 years instead of 1, improved survival."

"We are looking at 92% in the 3-year group, and that is very high," said Dr. Joensuu. "We are making substantial improvement here."

View the complete commentary by Kathy D. Miller, MD, and read the original Medscape News story on this trial.

6. New Hope for Patients With Refractory Lymphoma

The experimental agent brentuximab vedotin, which has shown strong responses in patients with resistant and refractory Hodgkin lymphoma, was the first drug approved for lymphoma in 30 years. The results were reported at the 52nd annual meeting of the American Society of Hematology by Robert Chen, MD, Assistant Professor at the City of Hope National Medical Center in Duarte, California.[5] The data come from a single-group multicenter study of 102 patients, all of whom had failed autologous stem cell transplantation and a median of 4 chemotherapy regimens (range, 1-13). The median age of patients was 31 years (range, 15-77 years).

Brentuximab 1.8 mg/kg was administered as a 30-minute outpatient intravenous infusion once every 3 weeks for up to 16 cycles of therapy (median, 9 cycles).

Responses were "dramatic," Dr. Chen said. The objective response rate was 75%, and tumor reduction was demonstrated in 94 patients (96%). Around one third of patients (34%) achieved complete remission.

In August, the US Food and Drug Administration (FDA) granted accelerated approval of brentuximab vedotin infusion for the treatment of relapsed or refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma, as reported at the time by Medscape.

"Why are we so excited about this?" asked Bruce D. Cheson, MD, Professor of Medicine, Georgetown University, Washington, DC, in a Medscape commentary. "Not only is this a great drug, it is also a proof of concept. We now have demonstrated that you can take an antibody and link it strongly to a poison. It will get in the cells and kill them, without doing much damage to the rest of the body. This will be one of many to follow in its footsteps."

View the complete commentary from Bruce D. Cheson, MD, and read the original Medscape News story.

5. Improved Survival in Metastatic Pancreatic Cancer

A chemotherapy combination provided the best survival time ever reported in metastatic pancreatic cancer, according to a study from French researchers, but the combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) was considerably more toxic than gemcitabine. Data from the study, which were first presented at the 2010 annual meeting of ASCO® and reported by *Medscape Medical News* at that time, were published in May in *The New England Journal of Medicine*.[6] Although the data are largely the same, the published paper includes new information on quality-of-life measures, said lead author Thierry Conroy, MD, from the Centre Alexis Vautrin, Vandoeurve les Nancy, France.

Gemcitabine, used alone or in combination with other agents, has been the "reference regimen" for advanced pancreatic cancer treatment for an extended period of time, according to Dr. Conroy and colleagues from 48 centers in France. However, the study authors propose that FOLFIRINOX is now a first-line option for patients with metastatic pancreatic cancer "who are younger than 76 years, and who have a good performance status (Eastern Cooperative Oncology Group score [ECOG] 0 or 1), no cardiac ischemia, and normal or nearly normal bilirubin levels."

"This is the first study to show substantial improvements in survival in advanced pancreatic cancer," said Alok A. Khorana, MD, Associate Professor and Vice-Chief of Hematology-Oncology at the University of Rochester, Rochester, New York, in a Medscape viewpoint. "It is unfortunate, however, that this gain occurs with an aggressive multichemotherapy regimen rather than with the addition of targeted therapy as many had hoped for. Although the efficacy of the regimen is clear and substantial, concerns about toxicity and tolerability are ongoing."

Read the complete Medscape News story on this paper and the complete viewpoint by Alok A. Khorana, MD.

4. New Standard of Care for High-Risk ALL

A regimen of high-dose methotrexate was found to be superior to the standard protocol of escalating methotrexate in children and young adults with high-risk B-precursor acute lymphoblastic leukemia. The results of a phase 3 trial, [7] which were presented at the 2011 ASCO® annual meeting, established a new standard of treatment for this population.

In a planned interim analysis, 5-year event-free survival for patients who received the high-dose regimen was 82% compared with 75% for those receiving the escalation protocol.

"We feel that it is the standard of care to receive high-dose methotrexate in this population," said lead author Eric C. Larsen, MD, Director of the Maine Children's Cancer Program and the division of pediatric hematology/oncology at the Barbara Bush Children's Hospital at Maine Medical Center in Portland, adding that "high-dose methotrexate will be incorporated in current and future Children's Oncology Group trials for children and young adults."

Read the complete Medscape News story on this paper.

3. Increased Survival in Metastatic HER2-Positive Breast Cancer

The first randomized trial to compare the novel agent trastuzumab emtansine (T-DM1) with standard therapy shows that it significantly increased progression-free survival in women with metastatic breast cancer.[8] The study was presented at the 2011 EMCC in Stockholm, Sweden.

"First-line treatment with T-DM1 was associated with a statistically significant improvement in progression-free survival and was also associated with a reduction in the risk for toxicity," said lead author Sara Hurvitz, MD, Director of the Breast Oncology Program, Division of Hematology/Oncology, University of California, Los Angeles.

Median progression-free survival was 14.2 months for women who received T-DM1 and 9.2 months for those who received standard therapy with trastuzumab plus docetaxel. The hazard ratio was 0.59, indicating that treatment with T-DM1 reduced the probability of disease progression or death by 41% compared with standard therapy, noted Dr. Hurvitz.

"These results validate the hypothesis that the unique targeted delivery of chemotherapy through T-DM1 may lead to an improved therapeutic index," she said.

Fabrice André, MD, PhD, Associate Professor at the Institut Gustave Roussy, Villejuif, France, as reported in a Medscape commentary, finds T-DM1 interesting for 3 distinct reasons. "The first is conceptual -- This is the first time that an immunoconjugate (a combination of a monoclonal antibody and a cytotoxic agent) has shown efficacy in cancer. It's a new concept, and we have the proof of concept. The second reason is the finding that immunoconjugate is safer compared with conventional chemotherapy. We had the presentation today, during which we heard that the frequency of grade 3 adverse events was lower in patients treated with T-DM1. The third reason it is so important is that these drugs can be delivered for a long time. Because of this prolongation of the treatment, we had a better progression-free survival, specifically in HER2-positive breast cancer."

Because T-DM1 is not toxic, it can be administered for a long period of time, which leads to long-term progression-free survival.

"We are entering in a new era with this trial," said Dr. André. "At the very beginning, to obtain a response the drug is not better. Once we have a response and once the drug is working, we can administer the drug for a longer time period and know that the patient is not going to present with progressive disease, but at the opposite end -- in patients treated with trastuzumab and docetaxel -- we have to stop both the chemotherapy agents. Then the patient is going to have a progressive disease. In terms of induction of the response, there is not any major difference

between T-DM1 and a combination of trastuzumab and docetaxel, but then duration of the response is very long. We are going through a scenario where we have induction with T-DM1, and once the patient has a response, then the response can be long lasting."

View the complete commentary from Fabrice André, MD, PhD, and read the original Medscape News story on this trial.

2. Lung Cancer Screening Comes of Age

The landmark National Lung Screening Trial,[9] which enrolled 53,000 persons,showed that screening with low-dose spiral CT reduced mortality from lung cancer by 20%. CT screening was compared with chest radiographs, which have not shown any mortality reduction in previous trials.

The study was accompanied by expressions of enthusiasm from the American oncology community. "It's gratifying. We've been looking for this kind of good news in lung cancer for a long time," Otis Brawley, MD, Chief Medical Officer at the American Cancer Society, told *Medscape Medical News*. "It's simply an amazing result with an immediate impact on this disease," Mark G. Kris, MD, Chief of Thoracic Oncology at Memorial Sloan-Kettering Cancer Center, reported in a Medscape commentary.

"Finally we have a screening test that meets that gold standard and has a substantial opportunity to decrease the death rate for lung cancer," said Dr. Kris. "In the group that was screened, all patients had smoked 30 pack-years, which is the equivalent of 1 pack per day for 30 years, 2 packs per day for 15 years, and so on. Based on these data, it makes sense to recommend screening with a low-dose helical CT for any person who has smoked 30 pack-years."

In November, the National Comprehensive Cancer Network in an updated set of guidelines came out in favor of lung cancer screening, recommending the use of low-dose CT screening for select patients at high risk for disease.

View the complete commentary by Mark G. Kris, MD, and read the original Medscape News story on this trial.

1. The Top Game Changer for 2011 in Oncology

Unprecedented Advances in Melanoma

In 2011, 2 studies and 2 drug approvals revolutionized therapy for patients with metastatic melanoma. Vemurafenib and ipilimumab quickly became household names after studies on their efficacies in metastatic melanoma were highlighted in the plenary session of the 2011 ASCO® annual meeting.

Vemurafenib. In a phase 3 study[10] that was accompanied by much praise and grand declarations, the targeted therapy vemurafenib was shown to dramatically improve progression-free and overall survival, compared with standard chemotherapy, in patients with advanced melanoma with no previous treatment.

Vemurafenib targets the V600E mutations in the *BRAF* gene, and an estimated 40%-60% of melanoma patients have this type of *BRAF* mutation.

The progression-free survival data constitute "an unprecedented level of difference," said lead author Paul Chapman, MD, from Memorial Sloan-Kettering Cancer Center.

This study is "practice changing," said Lynn Schuchter, MD, from the Abramson Cancer Center at the University of Pennsylvania in Philadelphia. Responses with the new oral therapy can be dramatic -- patients can have improvement within 72 hours of treatment, she said.

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