Highlights in Oncology 2012

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2012 has been a rich year in progress on cancer care. Many studies highlighted this year capitalised on the growing insight into the complexity of cancer to develop sophisticated treatment approaches, including combinations of targeted drugs for difficult-to-treat cancers and expanded use of targeted drugs to multiple forms of cancer sharing the same genetic alteration. This article is based on the clinical cancer advances 2012 article published by the American Society of Clinical Oncology and lists the most important advances made in the different fields of oncology that are most likely to impact daily clinical practice.[1]

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Breast cancer

Drug-antibody conjugate improves survival in HER2+ metastatic breast cancer

Results of a phase III EMILIA trial indicate that T-DM1, an experimental agent consisting of the antibody trastuzumab linked to the cytotoxic agent emtansine, outperforms the only current standard therapy for HER2+ metastatic breast cancer that fails to respond to trastuzumab. In EMILIA, 911 women with HER2-positive locally advanced or metastatic breast cancer who progressed despite standard trastuzumab therapy, were randomly assigned to T-DM1 or capecitabine plus lapatinib (CL). T-DM1 delayed the median time to disease progression compared to CL by more than three months (9.6 versus 6.4 months). Two years after treatment, the median overall survival (OS) rates for T-DM1 were also significantly higher for T-DM1 compared to CL (65.4% versus 47.5%). At interim analysis, the median survival times for T-DM1 and CL were 30.9 and 25.1 months respectively.[2]

Dual HER2-blocking in HER2+ breast cancer

Results of a phase III trial (N=808) reported this year, indicate that combining trastuzumab and chemotherapy (docetaxel) with pertuzumab, another anti-HER2 antibody, in previously untreated patients, may overcome or delay resistance to trastuzumab. The combination treatment significantly delayed disease progression compared to trastuzumab and docetaxel alone.[3] The median time to disease progression was 12.4 months for the control group versus 18.5 months in the pertuzumab group. Interestingly, adding pertuzumab did not result in substantially more toxicity.[3]

Adding everolimus to exemestane delays disease progression in postmenopausal ER+ advanced breast cancer

A randomised phase III trial presented this year compared the effectiveness of combination therapy with exemestane plus everolimus to the combination of exemestane and placebo in 724 women with ER+ advanced breast cancer, whose disease had progressed despite therapy with an aromatase inhibitor. Exemestane plus everolimus more than doubled the progression-free survival (PFS) from 4.1 months with exemestane placebo to 10.6 months. However, the addition of everolimus increased the overall toxicity of the treatment.[4] As such, careful observation of treated patients is necessary.[4]

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Blood and lymphatic cancer

Lenalidomide maintenance delays multiple myeloma recurrence

Two phase III trials reported this year, indicate that lenalidomide may be able to delay relapses in patients with multiple myeloma after stem-cell transplantation. In the first study, 615 patients aged younger than 65 years were randomly assigned to maintenance treatment with lenalidomide or placebo until relapse.

The median PFS in this study was 41 months with lenalidomide versus 23 months with placebo. After four years of follow-up, over 70% of patients were alive in both groups.[5] In the second study, 460 patients with multiple myeloma were randomly assigned to receive lendalidomide or placebo. The median PFS was 46 months in the lenalidomide group and 27 months in the placebo group. Lenalidomide also increased OS (35 deaths with the lenalidomide group versus 53 deaths with placebo).[6] Unfortunately, lenalidomide was also associated with more adverse effects and higher incidence of second cancers compared to placebo. Therefore, the risks and benefits of lenalidomide maintenance should be carefully assessed.

Gastrointestinal cancer

Neoadjuvant chemotherapy and radiotherapy double survival for oesophageal cancer

A phase III clinical trial to determine if treatment with chemotherapy and radiation therapy before surgery could improve the success of surgery and extend patient survival, randomly assigned patients with adenocarcinoma, squamous cell carcinoma, and large-cell undifferentiated carcinoma of the oesophagus or gastro- oesophageal junction to chemotherapy (carboplatin and paclitaxel) plus radiation therapy followed by surgery (N=178) or surgery alone (N=188).[7]

The preoperative treatment yielded substantial benefits with 29% of patients experiencing complete remissions. Moreover, median OS was longer (49 versus 24 months), and the death rate was 35% lower in patients who underwent preoperative treatment compared to those who had surgery alone. Interestingly, toxicities from this additional therapy were minor. These findings will likely change the standard of care for these patients, offering a curative option for many.[7]

Regorafenib prolongs survival in metastatic colorectal cancer

The phase III CORRECT study, evaluating if regorafenib would extend OS in patients with metastatic colorectal cancer, whose disease had progressed after all approved standard therapies, randomly assigned patients to receive regorafenib plus best supportive care (BSC) (505 patients) or placebo plus BSC (255 patients). An interim analysis of this trial demonstrated a notable improvement in median OS for regorafenib versus placebo (6.4 versus 5.0 months).[8] Based on these encouraging results, the study was unblinded to allow patients to switch from placebo to regorafenib.

Genitourinary cancer

Enzalutamide improves survival for men with chemotherapy-treated prostate cancer

Enzalutamide blocks androgen binding and translocation of the androgen receptor into the nucleus, as well as its attachment to DNA. A multinational phase III trial randomly assigned 1,199 men with castration-resistant prostate cancer (CRPC) who had previously been treated with docetaxel, to treatment with enzalutamide or placebo. Median OS for men treated with enzalutamide was 18.4 months versus 13.6 months for men who received placebo. At interim analysis, patients receiving enzalutamide had a 37% lower rate of death compared to those receiving placebo.[9] On the basis of these remarkable results, the study was unblinded .

Abiraterone acetate delays cancer progression in men with chemotherapy-naïve metastatic CRPC

Abiraterone acetate in combination with prednisone is currently approved for the treatment of men with CRPC, who have previously been treated with docetaxel. Results of a phase III multinational study, released this year, demonstrate that abiraterone acetate and prednisone may also benefit men with asymptomatic or minimally symptomatic, chemotherapy-naïve metastatic CRPC. In the study, 1,088 patients were randomly assigned to receive abiraterone acetate and prednisone or prednisone and placebo.[10] After 22 months of follow-up, abiraterone acetate was shown to improve PFS (11.1 months for abiraterone versus 5.6 months for placebo) and showed a strong trend towards prolonged OS. Furthermore, patients receiving abiraterone also had delayed onset of cancer-related pain and functional decline,

and the initiation of chemotherapy was postponed.[10] On the basis of these compelling results, the study was unblinded.

Radium-223 improves overall survival in CRPC metastasised to the bone

The randomised, phase III ALSYMPCA trial compared the efficacy of the alpha-emitting radiopharmaceutical ^{223}Ra (N=615) to placebo (N=307) in men with CRPC with two or more bone metastases. The median OS was 14.9 months in the ^{223}Ra group versus 11.3 months in the placebo-treated patients. Interestingly, ^{223}Ra was associated with only minor adverse effects. An updated analysis of the trial data showed that compared to placebo, ^{223}Ra reduced the risk of death by 30.5%, delayed the onset of skeletal complications by six months, and improved patients' quality of life.

Gynaecological cancer

Adding bevaciaumab to chemotherapy delays disease progression in platinum-resistant recurrent ovarian cancer

Previously reported trials demonstrate that adding bevacizumab to platinum-based chemotherapy prolongs PFS in patients with newly diagnosed platinum- sensitive recurrent ovarian cancer. This year, results of the phase III AURELIA trial demonstrate that adding bevacizumab to standard chemotherapy also benefits women with recurrent ovarian cancer resistant to platinum-based chemotherapy. In the trial, 361 women, who had received up to two prior treatment regimens, were randomly assigned to receive standard chemotherapy alone or chemotherapy plus bevacizumab. The median time to disease progression was 6.7 months for chemotherapy plus bevacizumab compared to 3.4 months for chemotherapy alone.[13]

Head and neck cancer

Cabozantinib delays disease progression in medullary thyroid carcinoma

Results of a phase III trial identify a potential new treatment option for advanced or metastatic medullary thyroid cancer (MTC). In the study, 330 patients with progressive, inoperable, locally advanced, or metastatic MTC were randomised between cabozantinib or placebo. Cabozantinib is a new targeted agent blocking growth of tumour blood vessels and metastases by inhibiting: MET, VEGFR-2 and RET. Approximately half of the patients in the trial at hand had RET gene alterations in their tumours. Cabozantinib prolonged the median PFS by over seven months compared to placebo (11.2 versus 4 months). Tumour shrinkage occurred in 28% of patients receiving cabozantinib and in none of those receiving placebo, with responses lasting a median of 14.6 months.[14] The drug is currently being explored in other cancer types that frequently harbour the proteins targeted by cabozantinib.

Lung cancer

Combination chemotherapy prolongs survival in certain types of advanced non-small cell lung cancer

Current guidelines recommend non-small cell lung cancer (NSCLC) patients with a performance score of 2 to be treated with one chemotherapy drug in order to slow disease progression while preserving their quality of life. However, recent phase III data indicate that patients with a performance score of 2 may live longer if treated with a combination of carboplatin and pemetrexed.[15] Patients with advanced NSCLC who had received no prior therapy were randomly assigned to receive pemetrexed (102 patients) or carboplatin and pemetrexed (103 patients). Tumour shrinkage was observed in 10% of patients receiving pemetrexed and 24% of patients receiving the two-drug treatment. The median OS was 5.6 months with pemetrexed versus 9.1 months with the combination.[15] These findings indicate that patients with NSCLC with a performance score of 2 can tolerate and benefit from combination chemotherapy, underscoring the importance of not undertreating this patient population.

Melanoma and skin cancer

Vismodegib blocks growth of basal cell carcinomas

Basal-cell naevus syndrome can cause the development of hundreds of basal-cell carcinomas in a single patient. There are currently no efficacious therapies for this syndrome. However, results of a phase II trial reported this year indicate that the new hedgehog inhibitor, vismodegib, is effective in this setting. In the study at hand, 41 patients were randomly assigned to receive vismodegib or placebo. During the eight-month follow-up, the drug significantly reduced basal-cell carcinoma tumour burden and blocked the growth of new tumours. Furthermore, no tumours progressed during treatment with vismo-

degib, and in some patients, all basal-cell carcinomas regressed.[16] Unfortunately, more than half of treated patients had to stop vismodegib because of adverse effects of the treatment (e.g. loss of taste, muscle cramps, weight loss, and hair loss).[16]

Promising treatment options for BRAF mutation positive metastatic melanoma

A phase III trial, comparing dabrafenib to dacarbazine in 250 patients with previously untreated, inoperable late-stage melanoma, demonstrated that patients treated with dabrafenib were more likely to respond to treatment and survive longer without their disease worsening. Tumour shrinkage occurred in 53% of patients treated with dabrafenib compared to only 19% treated with dacarbazine, and the median PFS was 5.1 and 2.7 months respectively.[17]

The phase III METRIC trial compared the efficacy of the MEK inhibitor trametinib alone to chemotherapy in 322 patients with BRAF-mutated advanced or metastatic melanoma. Treatment with chemotherapy alone resulted in a PFS of 1.5 months versus 4.8 months for patients receiving trametinib. Tumour shrinkage occurred in 24% of patients receiving trametinib and only in 7% of patients receiving chemotherapy.[18]

Finally, results of a phase I/II clinical trial (N=162) indicate that patients treated with a combination of the BRAF inhibitor dabrafenib and MEK inhibitor trametinib had lower incidence of skin rash and laesions compared to patients treated with either drug alone (7% versus 19%). Tumour shrinkage was observed in 76% of patients receiving combination therapy compared to 54% of those receiving single-agent therapy. The median PFS with the combination and single-agent therapy were 9.4 and 5.8 months respectively. Interestingly, skin laesions, a well-known adverse effect of vemurafenib, occurring in up to 25% of patients, were far less common with the dabrafenib plus trametinib combination.[19]

Sarcoma

Pazopanib prolongs PFS in patients with chemotherapy-resistant metastatic soft tissue sarcoma

In a phase III trial presented this year, 369 patients with advanced soft tissue sarcoma who progressed on standard chemotherapy, were randomly assigned to receive the tyrosine-kinase inhibitor (TKI) pazopanib or placebo.[20] The median PFS was 4.6 months in patients receiving pazopanib compared to 1.6 months in those receiving placebo. OS rates were similar in both treatment arms (12.5 months with pazopanib versus 10.7 months with placebo).[20] Despite the lack of major improvement in OS, this study represents the first positive randomised trial of a TKI for the treatment of non-GIST sarcoma.

Regorafenib delays progression in patients with advanced treatment-resistant GIST

An international randomised phase III trial provided highly promising results on the efficacy and safety of regorafenib in patients with advanced sarcoma who progressed on imatinib or sunitinib. Regorafenib was associated with a nearly four-fold increase in the median PFS compared to placebo (4.8 versus 0.9 months).[21] Based on these early signs of success, patients receiving placebo were allowed to switch over to regorafenib if their disease worsened. Regorafenib was well tolerated, with manageable adverse effects.[21] As such, regorafenib may be the first effective treatment option for patients with advanced GISTs resistant to treatment with imatinib and sunitinib.

Patient care

The antipsychotic drug olanzapine may control breakthrough chemotherapy-induced nausea and vomiting

Drugs that prevent chemotherapy-induced nausea and vomiting (CINV) have dramatically reduced its incidence and severity, but those drugs are not always sufficient, and a condition called breakthrough CINV continues to occur. Breakthrough CINV lowers patients' quality of life and may necessitate reductions in chemotherapy doses. In this light, a phase III trial demonstrated that olanzapine, an antipsychotic drug, may be helpful in controlling breakthrough CINV. The study enrolled patients receiving highly emetogenic chemotherapy who were treated with recommended drugs to prevent CINV before starting chemotherapy. Patients who developed breakthrough CINV (80 out of 205) were then randomly assigned to receive either daily olanzapine or daily metoclopramide.[22] During the observation period, 71% of patients receiving olanzapine had no vomiting versus 32% of patients receiving metoclopramide. Nausea did not occur in 67% and 24% of patients receiving olanzapine and metoclopramide, respectively.[22] As such, olanzapine

significantly outperforms metoclopramide for the treatment of breakthrough CINV, addressing an important unmet need for patients.

The antidepressant drug duloxetine relieves pain from chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common reasons patients stop chemotherapy early. Recent results from a phase III trial demonstrate the efficacy of duloxetine in the treatment of painful CIPN related to taxane- or platinum-based chemotherapy.[23] In the study, 231 patients with CIPN caused by prior treatment with oxaliplatin or paclitaxel were randomly assigned to receive duloxetine followed by placebo or placebo followed by duloxetine. Patients who received duloxetine over the initial treatment period had a greater average decrease in their pain score (-1.09) compared to those who received placebo (-0.33) in the initial period. Moreover, duloxetine was well tolerated, with the most common adverse effect being mild fatigue.[23]

References

1. Roth B, Krilov L, Adams S, et al. Clinical cancer advances 2012: annual report on progress against cancer from the American Society of clinical oncology. J Clin Oncol 2013;31(1):131-61.
2. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367(19):1783-91.
3. Baselga J, Cortes J, Kim S, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19.
4. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520-9.
5. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366:1782-91.
6. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 2012;366:1759-69.
7. Van Hagen P, Hulshof M, Lanschot J, et al. Preoperative chemoradiotherapy for esophageal orjunctional cancer. N Engl J Med 2012;366:2074-84.
8. Grothey A, Sobrero A, Siena S, et al. Results of a phase III randomised, double-blind, placebo-controlled, multicenter trial (CORRECT) of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients (pts) with metastatic colorectal cancer (mCRC) who have progressed after standard therapies. J Clin Oncol 2012;30(suppl 4; abstr LBA385).
9. Scher H, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187-97.
10. Ryan C, Smith M, De Bono J, et al. Interim analysis (IA) results of COU-AA-302, a randomised, phase III study of abiraterone acetate (AA) in chemotherapy-naive patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2012;30:281s(suppl; abstract LBA4518).
11. Parker C, Heinrich D, O'Sullivan J, et al. Updated analysis of the phase III, double-blind, randomised, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA). J Clin Oncol 2012;30:280s(suppl; abstract LBA4512).
12. Parker C, Coleman R, Nilsson S, et al. Updated survival, quality of life (QOL), and safety data of Radium-223 chloride (RA-223) in patientswith castration-resistant prostate cancer (CRPC) with bone metastases from the phase 3 doubleblind, randomised, multinational study (ALSYMCA). Presented at ESMO 2012, abstract 898PD.
13. Pujade-Lauraine E, Hilpert F, Weber B, et al. AURELIA: A randomised phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC). J Clin Oncol 2012;30:327s(suppl; abstract LBA5002).
14. Schoffski P, Elisei R, Müller S, et al. An international, double-blind, randomised, placebocontrolled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients (pts) with documented RECIST progression atbaseline. J Clin Oncol 2012;30:358s(suppl; abstract 5508).
15. Lilenabaum R, Zukin M, Pereira J, et al. A randomised phase III trial of single-agent pemetrexed (P) versus carboplatin and pemetrexed (CP) in patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) of 2. J Clin Oncol 2012;30:481s(suppl; abstract 7506).
16. Tang J, Mackay-Wiggan J, Aszterbaum M, et al: Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med 2012;366:2180-8.
17. Hauschild A, Grob J, Demidov L, et al. Dabrafenib in BRAF-mutated metastatic melanoma:A multicentre, open-label, phase 3 randomised controlledtrial. Lancet 2012;380:358-65.
18. Flaherty K, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF mutated melanoma. N Engl J Med 2012;367:107-14.
19. Flaherty K, Infante J, Daud A, et al. Combined BRAF and MEK inhibiton in melanoma with BRAF V600 mutations. N Engl J Med 2012;367(18):1694-703.
20. Van der Graaf W, Blay J, Chawla S, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379:1879-86.
21. Demetri G, Reichardt P, Kang Y, et al. Randomised phase III trial of regorafenib in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumour (GIST) progressing despite prior treatment with at least imatinib (IM) and sunitinib (SU): GRID trial. J Clin Oncol 2012;30:632s (suppl; abstract LBA10008).
22. Navari R, Nagy C, Gray S, et al. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy. J Clin Oncol 2012;30:582s(suppl; abstr 9064).
23. Lavoie Smith EM, Pang H, Cirrincione C, et al: CALGB 170601: A phase III double blind trial of duloxetine to treat painful chemotherapy-induced peripheral neuropathy (CIPN). J Clin Oncol 2012;30:570s(suppl; abstract CRA9013).