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What's New in Clinical Oncology?

Highlights from the 2009 ASCO Annual Meeting

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ABSTRACT This review summarizes the major advances in clinical oncology presented at the 2009 ASCO annual meeting, with emphasis on studies that are potentially practice-changing. Emerging new drugs are also discussed.

KEY WORDS: ASCO, clinical oncology.

The 45th Annual Meeting of the American Society of Clinical Oncology (ASCO) was held in Orlando, Florida from May 29 to June 2, 2009. It attracted nearly 30,000 cancer specialists from more than 100 countries. The theme of this year's meeting was "Personalizing Cancer Care". Approximately 4000 studies were presented at the meeting. Most of the studies focused on the testing of new drugs, new treatment approaches or strategies, and the predictive or prognostic value of molecular markers and molecular assays. As expected, there were a number of important studies which will impact current clinical practice. We reviewed the studies presented in the areas of lung cancer, breast cancer, colorectal cancer, gastrointestinal cancer, prostate cancer, gynecological cancer, and melanoma, and selected what we perceived as the most important or potential practice-changing findings. Emerging new drugs for some cancers were also discussed. All abstracts cited in this review are from the 2009 ASCO meeting proceedings[1,2].

Lung cancer

Maintenance therapy with targeted medicines for non-small cell lung cancer (NSCLC) may prolong survival

A phase III study of pemetrexed *vs.* placebo for stage IIIb/IV NSCLC after chemotherapy demonstrated a better overall survival for the treatment group, especially for patients with non-squamous NSCLC (15.5 *vs.* 10.3 months, $P = 0.002$) (Abstract CRA8000). The therapy was well tolerated and could be administered over a long duration without any significant accumulative toxicity. This is the first study to show a significant clinical benefit both in progression-free survival (PFS) and overall survival (OS) with the use of pemetrexed in the maintenance setting. Based on the data of this study, pemetrexed was approved by the FDA on July 2009 as maintenance therapy for metastatic NSCLC, specifically in patients with non-squamous histology in which disease has not progressed after 4 cycles of platinum-based first-line chemotherapy.

Two other studies compared erlotinib *vs.* placebo (SATURN) and bevacizumab combined with erlotinib *vs.* bevacizumab with placebo

(ATLAS) respectively (Abstract CRA8001, CRA8002). PFS was significantly improved in the treatment group with erlotinib in both studies for all patient subgroups (including those with squamous cell carcinoma), regardless of biomarker status including EGFR and KRAS, and no new safety issues were reported. These data support the use of maintenance therapy with targeted medicines in advanced stage NSCLC, though the erlotinib/bevacizumab regimen may raise an issue of cost-effectiveness.

Adjuvant chemotherapy for early stage NSCLC can prolong survival, while neoadjuvant chemotherapy did not show survival benefit in this setting

A phase III clinical trial (JBR10) was one of a number of clinical trials that established adjuvant cisplatin-based chemotherapy as a recommended treatment for completely resected NSCLC. An updated report was presented this year with long-term follow-up data. The survival benefit was further confirmed, though the benefit appeared to be confined to N1 patients: median OS 6.8 years *vs*. 3.6 years when comparing the chemotherapy arm the with observation arm. All patients appeared to benefit except those with tumors T > 4 cm (Abstract 7501). Notably, the previously reported high incidence of non-cancer deaths in the treatment group was not observed with long-term follow-up data. On the other hand, a multinational phase III trial (NATCH) of neoadjuvant therapy using taxol + carboplatin in early-stage NSCLC including stage I, II, T3N1 did not find a survival benefit (Abstract 7500). So far no prospective studies support neoadjuvant chemotherapy in early stage settings.

MSH2 and ERCC1 may be used to identify patients who can benefit from adjuvant chemotherapy

As cisplatin-based chemotherapy has proven its role in adjuvant settings, it is important to identify patients who can benefit from this treatment. Since the human MutS homolog 2 (MSH2) protein is required to repair cisplatin-DNA lesions, its predictive value was studied in the International Adjuvant Lung Trial from Europe (Abstract CRA7502). The study showed that chemotherapy prolonged survival in the MSH2 negative group (adjusted hazard ratio for death, 0.76; $P = 0.03$) but not in the MSH2 positive group (adjusted hazard ratio for death, 1.12; $P = 0.48$). In addition, the benefit of chemotherapy was decreased among patients with both positive MSH2 and ERCC1 (excision repair cross-complementing group 1). MSH2 and ERCC1 appeared to predict a long-term benefit from adjuvant cisplatin-based chemotherapy in patients with NSCLC.

EGFR mutation can be used to identify patients who will benefit from gefitinib

A multinational study from Asia (IPASS) demonstrated that EGFR mutations were a strong predictive biomarker for gefitinib when used for patients with adenocarcinoma (Abstract 8006). PFS was significantly improved in patients with positive EGFR mutations who were treated with gefitinib (9.5 *vs.* 6.3 months, $P < 0.0001$). In addition, EGFR gene copy number may predict a differential response to gefitinib. On the contrary, the KRAS mutation, a marker associated with outcome for cetuximab in colorectal cancer, did not show its predictive value in NSCLC patients treated with cetuximab (FLEX study, Abstract 8007).

Emerging new drugs

A phase III clinical trial (ZODIAC) on vandetanib + docetaxel *vs.* docetaxel alone, in recurrent NSCLC after failure of first-line chemotherapy, showed promising results (Abstract CRA8003). PFS was improved regardless of histology and biomarkers. Vandetanib is the first oral targeted agent to show improvement in PFS and quality of life when combined with standard chemotherapy for treatment of recurrent NSCLC. Another study investigated the synergistic effect of vorinostat with chemotherapy as the frontline treatment for advanced stage NSCLC (Abstract 8004). Vorinostat is an oral histone deacetylase inhibitor which was approved for the treatment of cutaneous T-cell lymphoma. The results demonstrated a higher response rate in the experimental group. Although the trend of survival favored vorinostate, it was not statistically significant. Celecoxib, a COX-2 inhibitor, was also studied with similarly disappointing results for advanced stage NSCLC (Abstract 8005). Perhaps it should be tested in selected patients based on the COX-2 level. A CALGB30801 Phase III trial using COX-2 index to select patients is in the planning stage and, hopefully, will provide an answer. PF-02341066, an oral agent targeting c-Met, demonstrated an overall response rate of 53% in EML4-ALK positive patients. EML4-ALK seems a promising marker for ALK inhibitors (Abstract 3509).

Breast cancer

Axillary treatment may be needed for patients with sentinel lymph node micrometastases

Detection of isolated tumor cells and micrometastases occurs frequently by sentinel node dissection. Its prognostic value, however, remains controversial. A retrospective study (MIRROR Study) from the Netherlands found a higher axillary recurrence rate in patients with micrometastases who did not receive axillary treatment after sentinel node dissection (5.0% *vs.* 1.0%); however, no significant increase was observed in patients with isolated tumor cells or negative nodes (Abstract CRA506). It appears that completion axillary treatment is necessary in patients with micrometastases.

Bevacizumab with different frontline chemotherapy regimens improves PFS in patients with metastatic breast cancer

Previous studies demonstrated that regimens of bevacizumab with taxanes (paclitaxel, docetaxel) in first-line setting improved PFS in patients with metastatic breast cancer. A phase III study (RIBBON trial) this year further confirmed that bevacizumab can improve PFS with different frontline chemotherapy regimens including capecitabine-, taxane-, or anthracycline-containing chemotherapy, though there is no benefit to OS (Abstract 1005).

Concomitant use of CYP2D6 inhibitors with tamoxifen: be cautious

Hepatic cytochrome P4502D6 (CYP2D6) inhibitors have been commonly coprescribed for patients treated with tamoxifen for hot flashes and depression. Since CYP2D6 is critical in converting tamoxifen to the active metabolite endoxifen, physicians are concerned about the potential negative impact of CYP2D6 inhibitors on tamoxifen efficacy. A retrospective study in the US using medical and pharmacy claims databases demonstrated that concomitant use of tamoxifen and moderate/potent CYP2D6 inhibitors significantly increased the risk of breast cancer recurrence (7.5% with no inhibitor *vs.* 14.0% with inhibitor, $P < 0.001$) (Abstract CRA508). On the other hand, a Dutch study using a similar approach did not find the association between CYP2D6 inhibitor use and breast cancer recurrence (Abstract CRA509). The conflicting results were probably due to the different sample size, endpoints, and the secondary database used for the study. Nevertheless, it is probably safer to avoid concomitant use of CYP2D6 inhibitors with tamoxifen, especially the potent inhibitors (fluoxetine and paroxetine), and moderate inhibitors (sertraline, cimetidine, amiodarone, doxepin, ticlopidine or haloperidol).

uPA/PAI-1 is a good predictor and prognosticator in patients with node-negative breast cancer

Urokinase-type plasminogen activator (uPA)/plasminogen activator inhibitor type 1 (PAI-1) plays a key role in tumor invasion and metastasis. A phase III trial demonstrated that uPA/PAI-1 levels significantly correlated with DFS and OS at 10 years in the absence of systemic therapy (10-year OS for patients with low uPA and PAI-1 *vs.* high: 88.9% *vs.* 77.5%, $P = 0.01$) (Abstract 511). Patients with high risk, as defined by uPA/PAI-1, received significant benefit from cyclophosphamide/methotrexate/5-fluorouracil (CMF) adjuvant treatment. uPA/PAI-1 was recommended for determining prognosis and deciding CMF-based adjuvant chemotherapy in node-negative breast cancer. An ongoing NNBC-3 Europe trial is exploring the optimal chemotherapy regimens for uPA/PAI-1 high-risk patients (Abstract 544). In another meta-analysis of 1637 patients with early stage breast cancer (T1-2, node-negative) from multiple institutions across Europe, the 70-gene assay (MammaPrint) was found to be both an independent prognosticator and a predictor for the benefit of chemotherapy (Abstract 512). Other studies (TAILORx and MINDACT) are evaluating the prognostic and predictive value of MammaPrint and Oncotype DX in the breast cancer patients who are node- and ER positive.

Emerging new drugs

Undoubtedly, one of the most exciting findings presented at the meeting involves Poly ADP Ribose Polymerase (PARP) inhibitors. The initial results showed very promising activity with no significant increase in toxicity in a subgroup of patients with BRCA1/2 mutations or with triple negative metastatic breast cancer. Two PARP inhibitors, Olaparib and BSI-201, were studied in a phase I and in a randomized phase II trial respectively (Abstract CRA501, Abstract 3). A high response rate of 41%, and a significant survival benefit (9.2 *vs.* 5.7 months) was observed. Although PARP inhibitors are still in their early clinical stage, they represent a new strategy of cancer drug development known as synthetic lethality. A phase III trial of 400 patients has been planned to investigate the efficacy of PARP inhibitors. Hopefully, this new class of drugs will soon be available for patients with BRCA1/2 mutations or with triple negative disease.

HER2 remains the target for some new drugs. One of the promising agents is T-DM1, a first-in-class HER2-antibody drug conjugate. A phase II study demonstrated a clinical benefit rate of 45% in patients with refractory metastatic breast cancer treated with T-DM1. It was well-tolerated with no dose-limiting cardiotoxicity (Abstract 1017). Pertuzumab and other TKIs targeting HER2 are also under investigation. It appears that more HER2 targeting agents will be available in a few years.

A phase III trial comparing ixabepilone + bevacizumab, nab-paclitaxel + bevacizumab, and paclitaxel + bevacizumab is underway, and some VEGFR-TKI alternatives including sorafenib and sunitinib are also under investigation in clinical trials for advanced stage breast cancer.

Colorectal cancer

The predictive value of KRAS mutation was further confirmed

Two retrospective studies assessed tumor samples from advanced CRC patients developing chemotherapy-refractory treated with cetuximab- or panitumumab-containing therapy to correlate mutational status and gene expression levels with outcomes (Abstract 4016, 4020). The results suggest that high EREG (epiregulin) expression plus wild-type KRAS may predict a cetuximab benefit in patients with previously treated metastatic colorectal cancer. Both KRAS and BRAF are strong negative predictors of cetuximab/panitumumab

outcomes. Two other prospective studies also confirmed the role of KRAS mutation in selecting patients who may benefit from panitumumab. Patients with wild-type KRAS are more likely to respond to therapy and have better survival outcomes in both the first-line and second-line settings (Abstract 4085, 4067).

Gene assays can identify high risk patients who may need adjuvant chemotherapy

So far, there are no standard criteria in selecting patients with stage II disease who need adjuvant chemotherapy. A gene assay, like Oncotype DX used in breast cancer, was developed for colorectal cancer. It was tested in a prospective study (QUASAR study) to evaluate recurrence risk after surgery and to identify patients who may benefit from 5-FU/Leucovorin chemotherapy. The study showed that the 7-gene defined recurrence score was associated with risk of recurrence, while the 6-gene defined treatment score did not predict any benefit of 5-fluorouracil (5-FU)/leucovorin therapy after surgery (Abstract 4000). This is the first study to show the clinical relevance of this type of gene assay, and it may help physicians determine who needs adjuvant therapy.

Resection of primary tumors in patients with metastasis may not be necessary

One question which remains unanswered in the management of stage IV colorectal cancer is whether it is necessary to remove the primary tumor in the absence of symptoms (bleeding, perforation, and obstruction) or in cases with resectable metastatic disease. A retrospective study was conducted at Memorial Sloan-Kettering Cancer Center to answer this question(Abstract CRA4030). Among 233 patients with synchronous metastasis and an unresected primary tumor who received oxaliplatin- or irinotecan-based, triple-drug chemotherapy (FOLFOX, IFL, or FOLFIRI) with or without bevacizumab as their initial treatment, 217 (93%) never required surgical palliation of their primary tumor. Sixteen patients (7%) required emergent surgery for primary tumor obstruction or perforation, and 10 patients (4%) required non-operative intervention (stent or radiotherapy), whereas 213 (89%) never required any direct symptomatic management for their intact primary. These data support the use of current combination chemotherapies without routine prophylactic resection as the appropriate standard practice for patients with neither obstructed nor hemorrhaging primary colorectal tumors in the setting of metastatic disease. A NSABP (the National Surgical Adjuvant Breast and Bowel Project) phase II trial is underway to address the same question, though it is focused on colon cancer only. The results will be available late this year.

Prophylactic treatment is better than reactive treatment for skin toxicity of EGFR targeted medicine in colorectal cancer

Panitumumab, a fully human monoclonal antibody targeting the epidermal growth factor receptor (EGFR), has been used as monotherapy for metastatic colorectal cancer. Its most common toxicity is skin toxicity. Although severe skin rash is a signal that the drug is working, it may cause pain, disfiguration, and may result in dose delay or even interruption of treatment. A clinical trial (STEPP Trial) was conducted to compare prophylactic treatment 24 hours before the first dose of panitumumab with reactive treatment after the skin toxicity appeared (Abstract CRA4027). Treatment includes moisturizers, sunscreen, topical steroid, and doxycycline. The results showed that prophylactic treatment significantly decreased the occurrence of skin toxicity (29% *vs.* 62%) and improved quality of life. This is the first randomized clinical trial demonstrating the advantage of prophylactic treatment over reactive treatment. Like the prophylactic strategy for other side effects of chemotherapy including nausea, vomiting, and diarrhea, this prophylactic approach probably will become the treatment of choice for severe skin rash in patients treated with panitumumab.

Bevacizumab is not beneficial in the adjuvant setting for stage II/III colon cancer

Bevacizumab has been successful in the setting of metastatic colon cancer, and it had been expected to play a role in the early stage of disease. However, the results of a highly anticipated clinical trial (NSABP protocol C-08) showed no significant benefit in this setting, and it turned out to be a negative trial (Abstract LBA4). The study was designed to evaluate the value of the addition of bevacizumab to mFOLFOX6 in the adjuvant setting for stage II/III colon cancer. The 3-year DFS was not significantly different in two groups (77.4% *vs.* 75.5%), though there was an early survival benefit favoring bevacizumab in the first 2 years. Longer administrations of bevacizumab beyond 1 year were proposed, but it may not be practical due to the cost and need of long-term treatment for a group of relatively elderly patients. Another similar study (AVANT BO17920) is ongoing, and it may provide conclusive results regarding the value of bevacizumab in the adjuvant setting for early stage colon cancer.

Oxaliplatin is not beneficial in rectal cancer

Two phase III studies explored oxaliplatin in rectal cancer. In one study (ACCORD 12/0405 Trial), oxaliplatin was added to the standard preoperative capecitabine/RT regimen for T3-4 rectal cancer. No improvement in tumor response or outcomes was found, but significant increased toxicity was observed (Abstract LBA4007). In another study, (STAR-01), similar results were found when weekly oxaliplain was added to the standard preoperative 5-FU/RT regimen as a radio-sensitizer in locally advanced rectal cancer (Abstract CRA4008). A clinical trial (NSABP R-04) which includes both of the above study designs with 4 arms is underway. Neverthe-

less, thus far, there is no evidence to support the addition of oxaliplatin to standard preoperative chemoradiotherapy for locally advanced rectal cancer.

Gastrointestinal cancer

Trastuzumab may become the first targeted therapy in HER2 positive gastric cancer

To date, no targeted agent has demonstrated clear efficacy in advanced gastric cancer, either as monotherapy, or in combination with chemotherapy. This will probably change with the ToGA trial, a phase III trial comparing cisplatin + fluoropyrimidine with cisplatin + fluoropyrimidine + trastuzumab in HER2 positive gastric cancer (Abstract LBA4509). In this study, 22% of 3807 patients were found to have HER2 expression. Patients with HER2 expression treated with trastuzumab showed a higher overall response rate (47.3% *vs.* 34.5%, $P < 0.01$), a longer median PFS (6.7 *vs.* 5.5 months, $P < 0.01$), and an improved median OS (13.8 *vs.* 11.1 months, $P < 0.01$). Notably, no additional toxicity, particularly cardiac toxicity, was observed. This is the first targeted therapy in gastric cancer to demonstrate a survival benefit. Trastuzumab may become a new therapeutic option for advanced gastric cancer patients.

Gemcitabine + cisplatin is better than gemcitabine alone for advanced biliary tract cancer

A clinical trial (ABC-02 trial) comparing gemcitabine + cisplatin *vs.* gemcitabine showed a better clinical benefit (PR + CR + SD 79.1% *vs.* 71.2%, $P = 0.26$) and a longer OS (11.7 *vs.* 8.3 months, $P = 0.002$) (Abstract 4503). Gemcitabine + cisplatin may become a new standard treatment for advanced biliary tract cancer.

Octreotide is active in patients with well-differentiated neuroendocrine tumors

Octreotide, a potent inhibitor of growth hormones, was investigated in a phase III trial in patients with well-differentiated neuroendocrine tumors (Abstract 4508). It was found that octreotide LAR significantly delayed tumor progression (15.6 *vs.* 5.9 months) predominantly in patients with a hepatic tumor load ≤ 10%. It was recommended that octreotide LAR be considered in newly diagnosed patients, especially those with limited hepatic burden, though its survival benefit remains undefined.

Prostate cancer

Pathologic characteristics and PSA doubling time (PSADT) may predict long-term prognosis

Two retrospective studies were conducted to investigate prognostic factors using long-term follow-up data (Abstract 5007, 5008). The presence of pathologic Gleason 8-10, seminal vesicle invasion, and lymph node metastases were found to be the prime determinants of prostate cancer-specific mortality (23%-49% risk), and a short PSADT was associated with early metastasis. The results suggest that Gleason scores and PSADT can be used as prognosticators and may also provide the background for appropriate selection of patients, treatments, and endpoints for future clinical trials.

Emerging new drugs

Two new drugs may provide hope for patients with castration-resistant prostate cancer (CRPC). A phase I-II study of MDV3100, a 2nd generation anti-androgen, demonstrated that it was a promising AR antagonist, active in CRPC both before and after chemotherapy (Abstract 5011). A phase III placebo-controlled trial in post-docetaxel CRPC is beginning this year.

Clusterin is induced by androgen deprivation in the prostate and confers resistance to radiation and cytotoxic drugs. OGX-011 is a 2nd generation phosphorothioate antisense oligonucleotide targeting the clusterin translation initiation site. A randomized phase II study demonstrated that OGX-011 inhibited its target resulting in a decline in serum clusterin, and was associated with improved OS (Abstract 5012). Further Phase III trials are needed to confirm its efficacy.

A prostatic acid phosphatase (PAP) as a targeted therapeutic vaccine, Sipuleucel-T (Provenge), and prostate specific antigen (PSA) as a targeted therapeutic vaccine, PROSTVAC-VF, also showed potential activity in metastatic CRPC in a phase II randomized trial (Abstract 5013). The overall 3-year survival was significantly prolonged in the experimental group (30% *vs.* 17%, $P = 0.016$). Further phase III studies are needed to confirm its efficacy. Although immunotherapies against CRPC failed to show an effect on pain, PSA levels or measurable disease, both Sipuleucel-T and PROSTVAC-VF demonstrated improved survival. It is likely that the first therapeutic vaccine will soon be available for prostate cancer treatment.

Gynecological cancer

Early treatment may not be necessary when an elevated CA125 is the only sign of recurrence/relapse of ovarian cancer

A phase III trial comparing the early treatment of recurrent ovarian cancer based on CA125 levels alone *vs.* the delayed treatment based on conventional clinical indicators found that early treatment did not improve overall survival, and had a negative impact on quality of life (Abstract 1). CA125 will probably remain an important marker for surveillance after first-line treatment, but treatment may not be needed when the elevated CA125 is the only sign of recurrence or relapse. Treatment can be postponed until symptoms or other physical or radiologic evidence of metastasis appears.

A new combined chemoradiotherapy as primary therapy for cervical cancer

A phase III trial comparing concurrent gemcitabine + cisplatin and radiation followed by adjuvant gemcitabine + cisplatin *vs.* concurrent cisplatin + radiation in patients with stage IIB to IVA carcinoma of the cervix demonstrated improved PFS (74.4% *vs.* 65.0%, $P = 0.029$) and OS (78.2% *vs.* 69.1%, $P = 0.022$) (Abstract 5507). This is the first randomized trial to compare combination of platinum-based chemoradiation to cisplatin alone, and it provides a new option for frontline treatment.

Melanoma

Emerging new drugs

A peptide vaccine targeting HLA A 0201 (gp100) was investigated in a multi-institutional phase III study in 185 patients with stage IV or locally advanced stage III cutaneous melanoma with HLA A0201 (Abstract CRA9011). Patients treated with HD IL-2 and vaccine had significant improvement in overall RR (22.1% *vs.* 9.7%, $P = 0.02$), PFS (2.9 *vs.* 1.6 months, $P = 0.01$), and also a trend of better OS (17.6 *vs.* 12.8 months, $P = 0.096$). This is the first phase III trial showing the clinical benefit of vaccination in patients with melanoma. About 50% of patients with metastatic melanoma have expression of HLA A0201. This vaccine may provide a platform for future clinical trials.

Molecular targeted therapy has also been investigated in patients with melanoma. A c-kit targeting agent, imatinib, showed encouraging effects on patients with positive c-Kit in a phase II study (Abstract 9001). Nevertheless, this subgroup of patients accounted for less than 1% of the overall patient population. A more exciting report was about PLX4032, an oral B-raf mutant targeting agent. In a proof-of-concept phase I trial, 5 out of 7 B-raf (+) patients had tumor regression (Abstract 9000). B-raf is the most common kinase mutation in melanoma (50%-60%). This study not only validated it as a therapeutic target, but also suggested that PLX4032 is a promising new drug for this subgroup of patients.

Summary

Targeted medicines and personalized therapies took center stage at the 2009 ASCO meeting, echoing the theme of personalized cancer care this year. Identifying key targets for cancer growth and metastasis and developing drugs to block or inhibit these targets has become the main approach for cancer research and treatment. Many phase I/II trials are exploring a wide variety of pathways, indicating a promising future for targeted medicine. Molecular markers/gene assays have become an integrated part of clinical trials. Some molecular assays have already been adopted in clinical practice for prediction of response and prognosis. This allows patients to receive the right treatment with the maximum benefit and to avoid the unnecessary costs and side effects from therapies that are unlikely to benefit them. Clinical advances presented at this year's ASCO meeting reflect the trend from one-size-fits-all medicine to personalized medicine in clinical oncology.

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