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Changing Paradigms in Clinical Oncology Research — Highlights from the 2011 ASCO Annual Meeting and Beyond

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ABSTRACT In this review, some important clinical advances presented at the 2011 American Society of Clinical Oncology (ASCO) meeting are summarized. Emerging trends in clinical oncology research are also discussed based on an analysis of the ASCO abstract database in recent years.

The American Society of Clinical Oncology (ASCO) annual meeting is the world's largest and most comprehensive gathering of professionals in the field of clinical oncology. It provides a great opportunity to learn the latest clinical developments and to identify trends in oncology research. In this review, some key findings presented at the 2011 ASCO meeting and emerging trends in clinical oncology research are summarized based on an analysis of the 2011 ASCO meeting proceeding and the ASCO abstract database in recent years.

Main clinical advances

This year, the main clinical advances were made in both common cancers as well as in some tumors previously less frequently presented.

Breast cancer

Breast cancer prevention among high-risk women has been a challenge. Use of the selective estrogen-receptor modulators tamoxifen and raloxifene had been approved for this purpose, but neither is being widely used mainly because of perceived concerns about their side effects. A landmark study has demonstrated that exemestane (an aromatase inhibitor) is more effective and safer than tamoxifen. It reduced the incidence of invasive breast cancer by 65% in high-risk postmenopausal women (LBA504). This study may reignite interest in breast cancer prevention, although awareness among physicians and cancer patients needs to be strengthened. Other agents, including two new selective estrogen-receptor modulators (lasofoxifene and arzoxifene), bisphosphonates, metformin, and aspirin, are also currently under investigation. Preventive therapy is expected to be integrated into wider strategies of breast cancer risk reduction, including combating obesity and increasing physical activity.

Prostate cancer

Treatment options for metastatic castration-resistant prostate cancer have expanded since 2002 with approvals of zoledronic acid, docetaxel,

sipulencel-T, cabazitaxel, denosumab, and abiraterone. Cabozantinib and radium-223 were reported to have promising results during the ASCO annual meeting, and there are even more novel agents in late-stage trials (e.g., Prostvac) (Abst 4516, Abst 4620). Most of the recent drugs are indicated for reduction of skeletal related events or for bone metastasis. The clinical management algorithm will be more complicated with these new agents, as each drug has its unique mechanism and is indicated at different time points of disease progression.

Lung cancer

Biomarker-driven cancer research and rationally designed drugs are well illustrated in lung cancer. In a large study of 1000 patients, 10 targetable driver mutations were identified in more than 50% of lung adenocarcinoma cases, and 97% of the mutations were found to be mutually exclusive (Abst 7506). The diagnostic information was used to select the corresponding targeted therapy including both established drugs and exploratory agents. If such target-driven strategy proves successful, more targeted drugs aiming at some niche indications in lung cancer and perhaps also in other tumors will surface in the near future. In fact, crizotinib (approved in August 2011) and MetMab were reported to be beneficial to lung cancer patients with ALK-positive and MET overexpression, respectively (Abst 7505, Abst 7507). Both markers account for a very small fragment of the overall lung cancer population. A study on erlotinib also emphasized the role of molecular markers. It demonstrated for the first time that erlotinib significantly improves progression-free survival (PFS) for patients with EGFR mutant lung cancer in the Caucasian population, as it does in the Asian population (Abst 7503).

Colorectal cancer

Multiple-pathway blockage is a rational approach to increase the likelihood of success for new targeted agents. In a phase Ib/II study, two novel combinations of agents targeting different pathways were explored, one of which, rilotumumab (monoclonal antibody directed against hepatocyte growth factor), demonstrated promising tumor response when combined with panitumumab in wild-type KRAS metastatic colorectal cancer (CRC) patients (Abst 3500).

Cetuximab is indicated for the treatment of patients with EGFR-expressing wild-type KRAS metastatic CRC. Patients with mutated KRAS respond poorly to cetuximab. However, a pooled study suggested that not all KRAS mutants are the same. A subset of patients with KRAS G13D mutations may benefit from cetuximab combined with chemotherapy (Abst 3511).

Ovarian cancer

With the success of avastin in lung cancer, CRC, renal cell carcinoma (RCC), and brain tumor, it has been aggressively tested in other tumors. A phase III study in patients with platinum-sensitive recurrent ovarian cancer showed that avastin can increase PFS by 4 months. A trend toward improved overall survival was also observed, although the results of the trial are still inconclusive (LBA 5007). Avastin may soon prove its value in recurrent ovarian cancer.

PARP inhibitors, a new high-profile class of agents, have been tested vigorously in different clinical settings. Although one of the leading agents, iniparib, failed in a pivotal trial for women with triple-negative breast cancer, PARP inhibitors have demonstrated some encouraging results in recurrent ovarian cancer. Olaparib, another similar but more potent agent, was also found to be able to improve PFS by 4 months in recurrent ovarian cancer (Abst 5003, Abst 5004). If the results can be confirmed in larger trials, PARP inhibitors could lead to a new treatment approach for recurrent ovarian cancer.

Melanoma

Melanoma made headlines again this year. Last year, a phase III trial for ipilimumab was the first to show a survival benefit in patients with advanced melanoma, which eventually led to its approval in March 2011. This year, vemurafenib demonstrated a very impressive improvement in survival compared with dacarbazine (PFS, 5.3 *vs.* 1.6 months) in patients who have BRAF mutations (LBA4). It was approved by the U.S. Food and Drug Administration soon after the conference. Ipilimumab is an immune stimulator intended for all patients, whereas vemurafenib is a BRAF inhibitor indicated for BRAF-positive patients, who comprise approximately half of the entire population of patients with melanoma. Due to their distinct mechanisms, these two drugs will likely play complementary roles rather than compete with each other in the management of melanoma. In fact, further studies of their combined or sequential use either are underway or have already been suggested.

RCC

RCC therapy has had six approved targeted drugs in the last 5 years: sorafenib, sunitinib, temsirolimus, everolimus, pazopanib, and bevacisumab. Now a new agent, axitinib, is likely to be added to the armament against RCC. Axitinib is an oral selective inhibitor of vascular endothelial growth factor receptors 1, 2, and 3. It has been compared with sorafenib in a head-to-head trial and the results demonstrated that axitinib improved PFS by 2 months (6.7 *vs.* 4.7 months) and was superior to sorafenib as second-line treatment for RCC (Abst 4503).

Sarcoma

Little progress has been made until recently for this group of rare and difficult-to-treat tumors. Targeted medicine again proved its role in different clinical

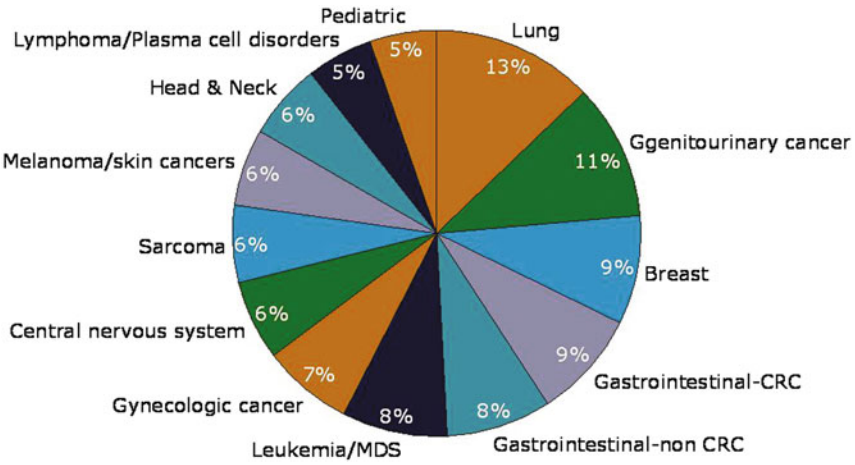

Fig.1. Distribution of abstracts by tumor site.

settings, including soft tissue and bone sarcomas. The targeted molecules ridaforolimus (a small-molecule rapamycin analogue and mTOR inhibitor) and pazopanib (a multi-targeted angiogenesis inhibitor) were found to be able to improve PFS for patients with sarcoma (Abst 10002, Abst 10005). They may provide new options for patients with this life-threatening disease.

Trends in clinical oncology research

Research efforts in different cancers

Although clinical studies presented at the 2011 ASCO meeting were focused on the big five tumors (i.e., lung, prostate, breast, colon-rectum, and stomach), the gaps between different tumors are becoming narrower and research efforts into which are being closely distributed (Fig. 1).[1]

Targeted medicine and immunotherapy/biological therapy in early clinical studies

Current oncology research and development efforts are focused on druggable pathway targets, continuing the shifting trend from cytotoxic to molecularly targeted medicine. An analysis of ASCO abstracts in different therapeutic categories showed that targeted agents (34%, including new targets/technologies, angiogenesis, and the PI3-Kt-mTOR pathway) and immunotherapy/biological therapy (24%) have dominated early clinical developmental studies (Fig. 2).[1] Many first-in-human or proof-of-concept studies were reported at the conference, and some encouraging results were cited for PARP inhibitors, JAK2 antagonists, BRAF antagonists, cMET antagonists, PI3-kinase antagonists, Hedgehog pathway antagonists, and proteasome inhibitors, among others.

Biomarker-driven studies and their applications

Modern biology has identified many potential targets for cancer therapy, and biomarkers have been increasingly integrated in clinical trials — even in the early stages. Such strategy may enrich patients with similar biological characteristics and facilitate proof-of-concept trials. In a phase I clinical program, 10 targetable driver mutations were tested among lung cancer patients; each patient was then matched with a corresponding targeted therapy (Abst 7506). The early results of the trial seemed encouraging. Recent approvals of many targeted drugs also show the importance of patient selection based on molecular markers for rationally designed targeted therapy. Moreover, the development of the accompanied molecular tests for the corresponding targeted agents has been integrated in many clinical trials.

Biomarkers are used for both patient selection and prediction of toxicity as well as symptom control. For instance, a study explored the correlation of serum hepcidin levels with chemotherapy-associated anemia and found that hepcidin measurements may help predict response to erythropoiesis-stimulating agents and supplemental iron (Abst 9031). Another study revealed that soluble TNF receptor 2 correlates with cognitive problems in breast cancer patients treated with adjuvant chemotherapy (Abst 9008). Such research may provide targets for future drug development with which to control such side effects.

In addition to biomarker-driven studies, tumor biology has been increasingly involved in clinical decision making. For example, many tumor-specific sessions in ASCO annual meetings are usually divided based on anatomy (local disease *vs.* metastatic disease); this year, breast cancer sessions were divided on the basis of biology (ER/PR or Her2-positive disease *vs.* triple-negative disease). This modification reflects an evolving understanding of the disease.

More informative early clinical trials

Cancer drug development is still a high-risk business. A recent study suggested that the overall attrition rate of oncology drugs from phase I to registration could be as high as 82%. The transition from phase II to phase III remains to be the most risky development step (attrition rate, 56%), and almost half of phase III trials have

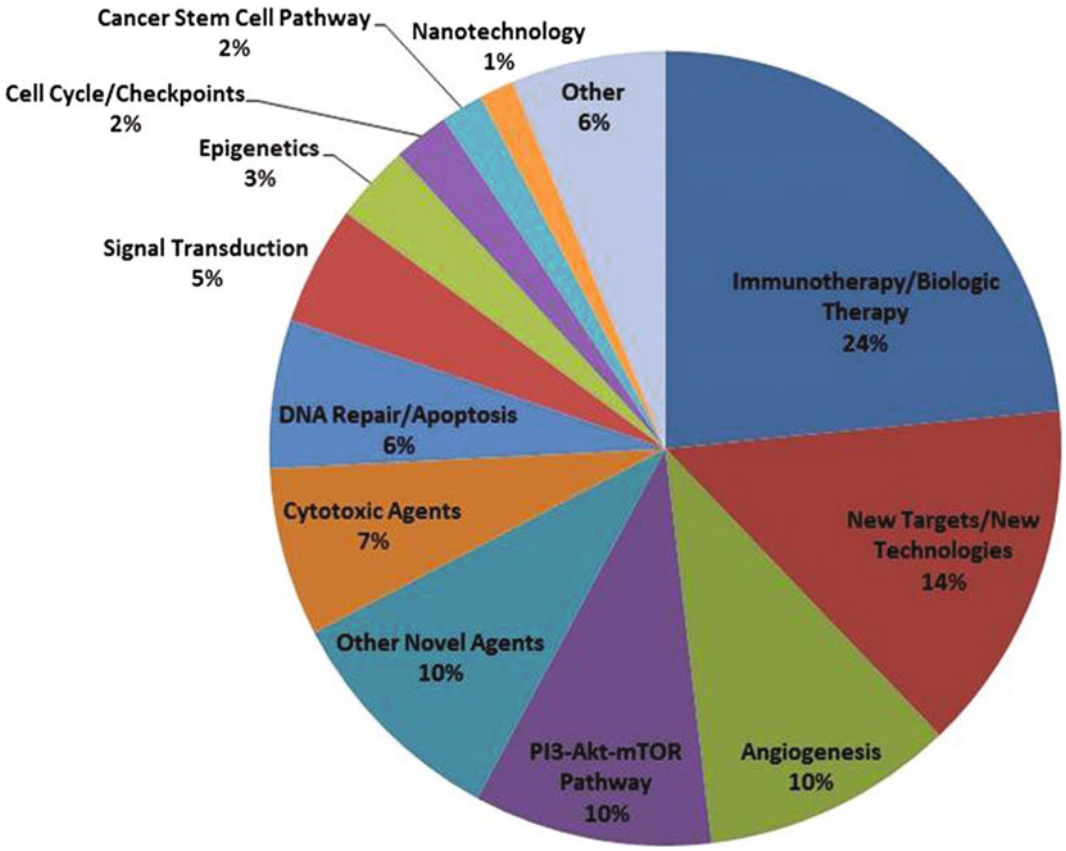

Fig.2. Distribution of abstracts by developmental therapeutic category.

failed.[2] Therefore, minimizing attrition rates is crucial in cancer drug development.

The primary purpose of a phase II trial is to determine whether a treatment regimen has sufficient activity to warrant testing in a phase III trial. Unfortunately, positive results from phase II trials frequently do not translate into positive phase III data, and the high failure rate in phase III oncology trials suggests that current phase II trials are not informative enough. Many efforts to optimize phase II trials have been made, and current trends in phase II trial design include the increased use of progression endpoints (e.g., disease control rate, PFS, time to progression, etc.) and randomization.[3] Randomized phase II trials may have lower error rates and greater predictive power for phase III results, and they may be more informative than single-arm phase II trials because of the hypotheses being tested, the variety of possible endpoints, and the opportunities for biomarker discovery.[4] A gradual but steady increase in randomized phase II trials has been observed at ASCO annual meetings in recent years (Fig. 3).[5]

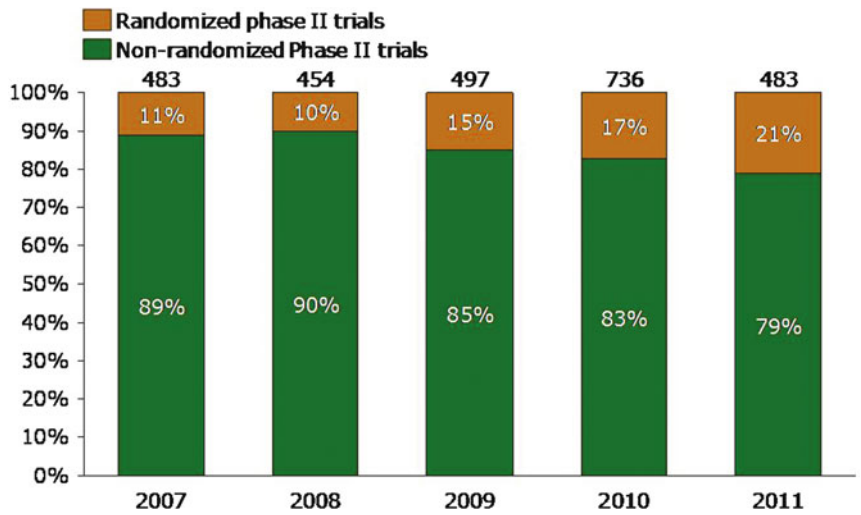

Fig.3. Steady increase in randomized phase II trials in recent years.

Greater collaboration

With better understanding of tumor biology, cancer patients are being grouped into greater subsettings based on their genomic/molecular profiles. This means that, in reality, every cancer may be a rare or orphan disease, and it is difficult or even impossible for one center to accrue enough patients within a reasonable period for a large clinical trial with so many competing pipeline agents around. Greater collaboration is needed to conduct clinical trials more efficiently, and studies involving multiple institutions or multiple countries have been increasingly presented at the recent ASCO meetings.

Summary

The genomic era has profoundly changed the paradigms of clinical oncology, including cancer care, clinical research, and pharmaceutical research and development. The studies presented at this year's ASCO meeting collectively illuminated the theme for 2011 (*Patients, Pathways, Progress*) which continues the trend of personalized medicine. Improved understanding of tumor biology, rationally designed targeted agents, novel approaches, and optimized study designs will help early clinical trials become more informative and increase the success rates for phase III trials. With the record six new approvals in oncology by the U.S. Food and Drug Administration thus far, this year is deemed to be an unusually productive year for cancer researchers, and a more fruitful future is expected in oncology drug development.

Conflict of Interest Statement

No potential conflicts of interest were disclosed.

References

1 ASCO proceeding, 2011.
2 Walker I. & Newell H. Do molecularly targeted agents in oncology have reduced attrition rates? Nature Rev. Drug Discov, 2009; 8: 15–6.
3 Solit DB, Tangen C, and Lara Jr PN. Developing and implementing more informative phase II oncology trials. ASCO educational book 2011; 84–88.
4 Sharma MR, Stadler WM, and Ratain MJ. Randomized phase II trials: a long-term investment with promising returns. J Natl Cancer Inst. 2011; 103: 1093–100.
5 ASCO online abstract database 2007–2011 (http://www.asco.org/ASCOv2/Meetings/Abstracts).