FLEX data, KRAS and ERCC1 testing in oncology

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Chicago seems the perfect conference city to visit for several days at the beginning of the summer, and one good aspect of this year's conference was that there were no dominant data presentations – instead there was something for everyone. Clinical oncology has struggled for decades with the predicament of the toxicity of chemotherapy for the treatment of malignant disease. Some patients benefit substantially from treatment with new and expensive drugs, whereas others suffer the toxic effects without obtaining real benefit. The use of molecular markers to help identify who may benefit and who may not is one of the most exciting new areas of study in oncology.

Nine questions about FLEX

Following on from several Phase II trials in this setting, Robert Pirker (Medical University of Vienna, Austria) presented a randomized, multicenter, Phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of 1125 patients with advanced non-small-cell lung cancer (NSCLC) across histological types including squamous disease (Abstract 3 [101]). Cetuximab plus CV demonstrated superior survival over CV alone in patients with advanced EGFR-detectable NSCLC. There was a remarkable difference between the outcome of Asian and Caucasian patients, with the former living longer. This is the first study to demonstrate a survival benefit of an EGFR-targeted agent in combination with platinum-based chemotherapy in advanced first-line NSCLC, irrespective of histology.

The first question about these data that Thomas Lynch (Massachusetts General Hospital, MA, USA) raised concerned safety: in the cetuximab arm, there was a rate of 22% febrile neutropenia versus 15% in the chemotherapy arm, which was unacceptably high. Second, what can we learn regarding the impressive survival in the Asian patients? Here, the percentage of non-smokers was very high, and there was an imbalance in the use of tyrosine kinase inhibitors after this trial. Third, why is progression-free survival (PFS) the same. One explanation is that as patients receiving cetuximab are treated weekly, there were more assessments and more care. A more likely explanation is an imbalance of second-line treatment, which suggests that PFS is imperfect for assessing treatment success and overall survival is the gold standard. Fourth, what about maintenance cetuximab in some patients? Here, the boundaries between first- and second-line therapy are blurred. Early docetaxel, pemetrexed and Tarceva® may be beneficial, but weekly cetuximab is inconvenient and costly, and 80% of eligible patients received maintenance. Fifth, why does cetuximab in combination with chemotherapy, unlike oral tyrosine kinase inhibitors, have a survival advantage. As the reviewer said simply, they are different molecules. Sixth, is selection using immunohistochemistry important? The intensity of staining does not correlate with outcome, but negative staining rules out nonresponders. Seventh, are there useful biomarkers here such as FISH or EGFR copy number? Unfortunately, we

still lack randomized data. Eight, is a 1.2-month improvement in overall survival really worth it (an age-old question that is broadly applicable)? A course of 18 weeks of cetuximab treatment costs approximately GB£30,000 for the average patient, translating to over GB£300,000 per year of life saved. With bevacizumab, the survival benefit was 2.5 months, so the final question was where does cetuximab fit into our therapeutic paradigm? There are 12,073 patients in other recent randomized studies and only two have shown a survival benefit – the hazard ratio in the First-Line in Lung Cancer with Erbitux (FLEX) trial (0.871 [95% CI: 0.762–0.996]) and p-value (0.441) were marginal, so cetuximab should probably be reserved for bevacizumab-ineligible patients or those with squamous cancers.

To KRAS or not to KRAS

Edwin van Cutsem (University Hospital Gasthuisberg, Leuven, Belgium) presented KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer treated with folinic acid, fluorouracil and irinotecan (FOLFIRI) with or without cetuximab (Abstract 2 [101]). Previously, efficacy analyses of the randomized Phase III Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYSTAL) trial have shown a significant improvement in PFS, overall response and curative surgery rate when adding cetuximab to FOLFIRI in the first-line treatment of metastatic colorectal cancer, although, as for FLEX, p-values were close. KRAS mutants were detected in 35.6% (192 out of 540) of patients with evaluable samples, and a statistically significant difference in favor of cetuximab was seen in KRAS wild-type patients for PFS ($p = 0.0167$) and best overall

response (59.3% [cetuximab + FOLFIRI] vs 43.2% [FOLFIRI]; $p = 0.0025$). In fact, the benefits of cetuximab here in general were confined to patients with KRAS wild-type, demonstrating the predictive value of this test, data that should now be applied to the adjuvant setting. Other studies, such as the Orbofiban in Patients with Unstable Coronary Syndromes (OPUS) experience (Abstract 4000 [101]) and preliminary Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) data (Abstract 4129 [101]), supported these personalized data.

ERCC1

Polymorphisms in ERCC1, involved in nucleotide-excision repair of platinum-induced damage, appear to be associated with PFS and overall survival in patients treated with platinum-based combination therapy. Previously, it has been shown that patients with completely resected NSCLC and ERCC1-negative tumors appear to benefit from adjuvant cisplatin-based chemotherapy, whereas patients with ERCC1-positive tumors do not [1,2]. ERCC1 is also the other half of the equation in colon cancer (choosing between folinic acid, fluorouracil and oxaliplatin [FOLFOX] and FOLFIRI therapy), with KRAS predicting efficacy of cetuximab or pemetumumab, and Gail Eckert (University of Colorado Cancer Center, CO, USA) pointed this out in the discussion of the FLEX-CRYSTAL data. Overall, there was a large number of presentations (Abstracts 5540, 5575, 5587, 8033, 11042, 16013 and 21050 [101]), including three papers from Novartis, validating that ERCC1 was predictive of the outcome of platinum-based therapy in colon and ovarian cancers, and showing that a series of genes, such as *VEGFR1* and *HIF1*, correlate with responses to their small-molecule drugs, such as PTK. Response Genetics (CA, USA), who are able to perform full Affymetrix® arrays on paraffin-embedded tissue, also validated (in a Southwest Oncology Group study over 3 years) that *TS* gene levels correlated with outcome to 5-fluorouracil/radiation in rectal cancer (Abstract 4115 [101]).

Small molecules versus monoclonal antibodies

While bevacizumab, trastuzumab and, to a lesser extent, cetuximab continue to produce impressive data, this year's monoclonal antibody pipeline presentations showed limited efficacy and, in many cases, pronounced toxicity. This was particularly true for the two CTLA-4-binding antibodies, ipilimumab and tremelimumab. Numerous abstracts (notably 3021, 9022, 9025 and 9009 [101]) and some Phase III data were presented (LBA9011 and 9010 [101]) for these molecules, which are designed to break tolerance. Autoimmune reactions, including colitis/diarrhea, were common but, surprisingly, prophylactic budesonide did not reduce these in a Phase III study (Abstract 9010), as presented by Jeffrey Weber (Lee Moffitt Cancer Institute, FL, USA). Most patients had at least one adverse event but, more importantly here, there did not appear to be any PFS or overall survival differences in intent-to-treat analyses, although long-term durability is often observed in the small proportion who do respond, even if they have progression elsewhere. New response-rate criteria were proposed by F Stephen Hodi (Dana Faber Cancer Institute, MA, USA) (Abstract 3088 [101]) to clarify the role of these agents, but this does not bode well for their future.

Following last year's success of sorafenib in hepatocellular carcinoma, Robert Figlin (UCLA, CA, USA) presented the overall survival with sunitinib versus IFN- α as first-line treatment of metastatic renal cell carcinoma (Abstract 5024 [101]). It was already known that in a randomized Phase III trial, sunitinib demonstrated statistically significant improvement in PFS and objective response rate compared with IFN- α as first-line therapy in metastatic renal cell carcinoma patients ($p < 0.001$) [3], but the median overall survival had not been reached for analysis. In a very positive presentation discussing that the standard of care changed during the study and that there were numerous crossovers confounding the analysis, the presenter seemed to

neglect to mention that in an intent-to-treat analysis, the p -value for overall survival was 0.051. Things are not always as good as they seem, despite the weather being sunny by this stage!

Unlike the KRAS or ERCC1 data in other tumor types, there are no biomarkers that appear to be useful here ... yet.

Adjuvant breast cancer

While debates continue regarding BCRG001 versus TACT1 and the benefits of Taxotere®, the GEICAM group, based in Spain, conducted a randomized Phase III study of adjuvant chemotherapy for high-risk, node-negative breast cancer comparing docetaxel, doxorubicin, and cyclophosphamide (TAC) with fluorouracil, doxorubicin and cyclophosphamide (FAC) (Abstract 542 [101]). Patients had at least one high-risk St Gallen 1998 criterion (grade II/III; size >2 cm; age <35 years; hormone-receptor negative) and, while TAC produced significantly more hematologic toxicity than FAC, no toxic deaths were reported. With a median follow-up of over 5 years, in 1059 patients randomized, adjuvant TAC was associated with a significant improvement in disease-free survival (DFS) compared with FAC (HR: 0.66; 95% CI: 0.46–0.94; $p = 0.0202$), with manageable toxicity, especially when G-CSF is used prophylactically. As for most adjuvant studies in breast cancer, too few survival events have occurred.

Michael Gnant (University of Vienna) presented (LBA4 [101]) the first efficacy results of a trial of adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with hormone-responsive, stage I and II breast cancer. In 1081 randomized women, there was no significant difference in DFS between tamoxifen and anastrozole, but the addition of zoledronic acid (4 mg once every 6 months) to adjuvant endocrine therapy significantly prolonged DFS and recurrence-free survival compared with adjuvant endocrine therapy alone in premenopausal women with

endocrine-responsive breast cancer. Martine Piccart (University of Brussels, Belgium) cautioned against drawing too many conclusions from a single trial, and the results of Robert Coleman's (Weston Park Hospital, Sheffield, UK) Adjuvant Zoledronic Acid Reduce Recurrence (AZURE) study are eagerly awaited.

Conclusion

Chicago has been a great venue and we will see how Orlando (FL, USA) measures up next year. We are very fortunate to attend these educational meetings and on a personal note, I can recommend going to sessions concerned with tumor types one does not normally follow.

Future perspective

Physicians have long attempted to harness maximum efficacy with minimum toxicity from bench-to-bedside therapies. Predictive testing is now assuming increasing importance throughout oncology, as opposed to simple prognostication. The incorporation of Oncotype Dx™ into American Society of Clinical Oncology guidelines for breast cancer therapy, telling physicians not how or when to give chemotherapy but, importantly, when not to treat, is a major step forward. KRAS and ERCC1 testing will now become mandatory over the next few years, selecting patients for cetuximab and platinum-based therapies, respectively,

in lung cancer. Their importance in other tumor types is being established as we approach an era of personalized therapy to minimize toxicity and enhance responses.

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Executive summary

- For the first time, the First-Line in Lung Cancer with Erbitux (FLEX) data showed a survival benefit for an EGFR-targeted agent in combination with platinum-based chemotherapy in advanced first-line non-small-cell lung carcinoma, including squamous histology.
- There are many questions regarding these data, not least of all how a change in progression-free survival is not translated to a change in overall survival.
- The cost of therapies such as cetuximab in this setting may be prohibitive, and bevacizumab is likely to remain the gold standard.
- The benefits of cetuximab are confined to patients with a KRAS wild-type, and this has implications for adjuvant and other studies.
- ERCC1-negative tumors benefit from platinum therapies.
- There do not appear to be useful biomarkers in determining responses to the newer small molecules and other antibodies or taxane-based chemotherapy.

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Website

101. American Society of Clinical Oncology website
www.asco.org/

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