Latest therapeutic advances from the ASCO 2010 Annual Meeting

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This year's Annual Meeting of the American Society of Clinical Oncology (ASCO), held in Chicago, 4–8 June, featured several very interesting presentations on advances in drug treatment of various cancers.

Eribulin increases survival in metastatic breast cancer

Eribulin mesylate is derived from marine sponge and is described as a microtubule dynamics inhibitor that affects cell division. Christopher Twelves (Leeds Institute of Molecular Medicine and St. James's Institute of Oncology in Leeds, UK) and colleagues reported results from a phase III open-label, randomized multicentre trial (EMBRACE) showing that eribulin extended median overall survival (OS) by approximately 2.5 months in women with locally recurrent or metastatic breast cancer (MBC) already heavily treated with conventional therapies [Twelves *et al.* 2010]. This was an international, multicentre trial and compared eribulin with real-life physician's choices of treatment among women with MBC who had received an average of four prior chemotherapy drugs (e.g. anthracyclines or taxanes). The study comprised 762 MBC patients who were randomized 2:1 to receive either eribulin (1.4 mg/m² 2–5 min IV bolus on days 1 and 8 of a 21-day cycle) or treatment of physician's choice: almost always another chemotherapy. Median OS (primary endpoint) was 13.1 months in the group who received eribulin compared with 10.7 months for those who did not receive the drug ($p=0.04$, hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.66–0.99). Grade 3/4 treatment-related adverse events with eribulin included asthenia/fatigue (7.6%), neutropenia (44%) and peripheral neuropathy (8.4%), and 10% of patients experienced treatment-related serious adverse events (12% with and 7% with no eribulin). Thus, eribulin was

shown to improve OS significantly with a manageable tolerability profile. The author commented that this treatment offers hope for a standard treatment in such heavily treated patients.

Paclitaxel plus carboplatin improves survival in advanced non-small cell lung cancer in the elderly

Professor Elisabeth Quoix (University Hospital, Strasbourg, France) and colleague presented results of a Phase III randomized, multicentre trial showing that combining paclitaxel and carboplatin significantly increased OS and progression-free survival (PFS) in patients aged 70–89 years with advanced non-small cell lung cancer (NSCLC) when compared with standard single-agent therapy [Quoix *et al.* 2010]. This is an important finding as studies in older patients are relatively rare and they are often given less-aggressive treatment than younger patients [Maione *et al.* 2010]. The study compared 3-weekly single-agent therapy (gemcitabine 1150 mg/m² or vinorelbine 30 mg/m², days 1 and 8) with carboplatin (AUC 6 every 4 weeks) plus paclitaxel 90 mg/m² (days 1, 8 and 15) doublet. Five cycles of single-agent and four cycles of the doublet were to be given. The study was initially planned to include 520 patients but was stopped when an interim analysis of 313 analysed patients showed OS was significantly longer in the combination group. At the conference, Professor Quoix presented final results from 451 patients. Mean survival time was 6.2 months (95% CI 5.3–7.4) and 1-year survival was 26.9% (95% CI 21–33.1) with single-agent therapy; however, doublet therapy significantly improved median survival by 4 months (10.3 months, 95% CI 8.3–13.3) and 1-year survival was 45.1% (95% CI 38.2–51.8), $p=0.00004$. The combination therapy had

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acceptable toxicity; however, data from the 313 patients found that the group receiving the combination regimen experienced moderate-to-severe neutropenia more frequently than the single-agent group (47.8% versus 12.2%). The authors concluded that paclitaxel plus carboplatin provides a significantly longer survival in elderly patients with advanced NSCLC than current single-agent therapy, with acceptable toxicity, and showed that a more intensive regimen may be given to such patients.

Crizotinib produces a high response rate in NSCLC patients with a specific ALK gene alteration

The investigational anaplastic lymphoma kinase (ALK) inhibitor, crizotinib, has been studied in an expanded Phase I clinical trial by Yung-Jue Bang and colleagues (Seoul National University, Korea) [Bang *et al.* 2010]. They found that approximately 90% of patients with advanced NSCLC with a specific form of the ALK gene responded to crizotinib therapy and more than half experienced tumour shrinkage. The ALK gene fuses to other genes and promotes lung cancer cell growth by encoding the production of the tumour-specific protein, ALK, an enzyme critical for cancer cell growth and development. About 1 in 20 lung cancer patients in the United States may have ALK-positive NSCLC. The study assessed crizotinib (250 mg twice daily orally) in patients with ALK+ NSCLC (mostly adenocarcinoma and nonsmokers or former smokers). To date, 50 of 76 treated patients have been evaluable for response. Nearly all (87% at 8 weeks) responded to treatment and experienced tumour shrinkage or disease stabilization. Among those, 57% had tumour shrinkage. The median duration of treatment was approximately 6 months.

These initial results are dramatic compared with what would be expected with standard chemotherapy for patients with metastatic disease. The next stage is a randomized Phase III trial (PROFILE-1007), which has begun, comparing crizotinib with standard second-line chemotherapy.

Ipilimumab improves long-term survival in previously treated advanced melanoma

Melanoma is one of the most deadly forms of cancer, and over the past three decades,

melanoma incidence has climbed faster than any other cancer type. Advanced melanoma is extremely difficult to treat; however, Steven O'Day and colleagues (The Angeles Clinic and Research Institute, Santa Monica, CA, USA) have reported results from a phase III clinical trial and found that patients with advanced, previously treated melanoma who received ipilimumab lived 34% longer than those who received the gp100 peptide vaccine [O'Day *et al.* 2010]. Ipilimumab is a monoclonal antibody that is administered intravenously. It is unlike other treatments that target the cancer cell. Instead, it activates T cells, which then actively destroy melanoma cells. The study involved 125 centres internationally and patients with advanced (stage III/IV) melanoma were randomized 1:3:1 to ipilimumab (3 mg/kg every 3 weeks $\times$ 4 doses) plus placebo (137 patients), ipilimumab plus gp100 (peptides 209–217[210M] and 280–288 [288V]; 1 mg every 3 weeks $\times$ 4 doses; 403 patients), or gp100 plus placebo (136 patients). There was no maintenance phase and the primary endpoint was comparison of OS between patients who received combination versus gp100 alone. Recipients of the vaccine alone lived a median of 6.5 months, which is comparable to placebo in past studies. The two groups that received ipilimumab each lived a median of 10 months, a significant improvement compared with vaccine alone. The 2-year survival was 24% among patients who received ipilimumab, 22% among those who received combination treatment but only 14% for those receiving gp100 vaccine monotherapy. Secondary endpoints such as disease control and progression were also better with ipilimumab than vaccine alone. Ipilimumab was well tolerated; however, 10–14% of ipilimumab patients experienced severe side effects, such as rash and colitis, compared with about 3% of the vaccine patients.

Cetuximab disappoints in stage III colon cancer patients with normal KRAS

Steven Alberts and colleagues (Mayo Clinic, Rochester, MN, USA) have reported that adding cetuximab to standard adjuvant chemotherapy in patients with stage III colon cancer and normal KRAS gene activity does not prolong their lives but does cause more side effects [Alberts *et al.* 2010]. Their phase III study was terminated early because of these results. This is a surprising result bearing in mind that cetuximab was previously found to improve

survival of patients with metastatic colon cancer whose tumours expressed normal KRAS. Patients with stage III disease and normal KRAS activity were randomly assigned to 12 biweekly cycles of oxaliplatin 85 mg/m² on day 1, with leucovorin 400 mg/m², 5-fluorouracil (mFOLFOX6), without (858 patients) or with cetuximab (902 patients) 250 mg/m² days 1 and 8, with cetuximab at 400 mg/m², cycle 1, day 1. Primary endpoint was 3-year disease free survival (DFS). Secondary endpoints included OS and toxicity. After a median follow-up period of 15.9 months, the 3-year DFS was similar in both groups (74.1% FOLFOX alone versus 73.3% FOLFOX plus cetuximab). The FOLFOX-only group had slightly better OS (87.3% versus 82.1%). Older patients who received cetuximab fared worse than patients under 70 years old who received cetuximab. Moderate-to-severe side effects were significantly greater in patients who received cetuximab, and fewer patients in this group were able to complete the full course of treatment owing to these toxicities. The authors concluded that this treatment should not be used in patients with resected stage III colon cancer.

Bevacizumab prolongs PFS in advanced ovarian cancer

For the first time, a phase III trial has found that an anti-angiogenic drug improves PFS in advanced ovarian cancer. This is a heartening result for the treatment of this hard-to-treat disease. Robert A. Burger and colleagues (Fox Chase Cancer Center, Philadelphia, PN, USA) conducted their international study on 1873 women (median age 60 years) with newly diagnosed stage III or IV ovarian, primary peritoneal or fallopian tube cancer who had undergone prior surgery to remove as much of the cancer as possible [Burger *et al.* 2010]. Patients were randomly assigned to one of three groups: (1) chemotherapy (IV paclitaxel 175 mg/m² plus carboplatin AUC 6, cycles 1–6) plus placebo cycles 2–22; (2) chemotherapy plus concurrent bevacizumab (15 mg/kg) cycles 2–6 plus placebo cycles 7–22; (3) chemotherapy plus concurrent bevacizumab cycles 2–6 plus maintenance bevacizumab cycles 7–22. Infusions were administered on day 1 of a 21-day cycle. The primary endpoint was PFS, and secondary endpoints included OS, safety, and quality of life. The results showed that standard chemotherapy plus bevacizumab with up to 10 months of

bevacizumab maintenance produced significantly longer periods of PFS (median of 14.1 months) than chemotherapy alone (median 10.3 months). Patients who received chemotherapy and bevacizumab followed by placebo maintenance had a median PFS of 11.2 months, which was not significantly different from those who received standard chemotherapy alone. Relative to standard chemotherapy alone, the hazard of first progression or death for the group receiving bevacizumab initially but not maintained was 0.908 (95% CI: 0.795–1.04, *p* = 0.16) but for those on bevacizumab maintenance it was 0.717 (95% CI: 0.625–0.824, *p* < 0.0001). Patients experienced bevacizumab-associated side effects (primarily hypertension and low white blood cell counts) of the type and frequency similar to what has been reported previously. This is the first anti-angiogenic agent to demonstrate benefit in this patient population and the results show that bevacizumab is an acceptable initial treatment option for patients with advanced ovarian, primary peritoneal and fallopian tube cancers.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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