HAEMATOLOGICAL CANCER

ECHELON-2 — brentuximab raises PTCL outcomes to new levels

Diverse peripheral T cell lymphoma (PTCL) subtypes are usually treated using cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or similar regimens, with generally poor results. CD30 expression is common in many PTCL subtypes and is pathognomonic of the systemic anaplastic large cell lymphoma (sALCL) subtype. Now, the excellent efficacy of the anti-CD30 antibody–drug conjugate brentuximab vedotin in this context has been demonstrated in the ECHELON-2 trial.

In this phase III trial, patients with previously untreated CD30$^+$ PTCL received brentuximab plus cyclophosphamide, doxorubicin and prednisone (A+CHP) or CHOP ($n = 226$ in both groups); 72% and 68% of patients, respectively, had sALCL. Strikingly, the median progression-free survival duration in the A+CHP group was more than double that in the CHOP group (48.2 months versus 20.8 months; HR 0.71, 95% CI 0.54–0.93; $P = 0.011$). Importantly, A+CHP treatment reduced the risk of death by 34% (HR 0.66, 95% CI 0.46–0.95; $P = 0.024$). The efficacy of A+CHP seemed to be greatest in sALCL subgroups and lowest in patients with angioimmunoblastic T cell lymphoma, although these histological subgroup analyses were underpowered.

A+CHP had a manageable toxicity profile that was mostly very similar to that of CHOP, with comparable rates of grade ≥3 adverse events (66% versus 65%), treatment discontinuation (6% versus 7%) and treatment-related deaths (3% versus 4%).

These results supported approval of A+CHP for the first-line treatment of CD30$^+$ PTCL via the FDA's Real-Time Oncology Review Pilot Program. Approval was granted on 16 November 2018, <2 weeks after completion of the licence application, thus rapidly transforming a treatment landscape that had for decades remained unchanged.

David Killock

ORIGINAL ARTICLE Horwitz, S. et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet* https://doi.org/10.1016/S0140-6736(18)32984-2 (2018)

BREAST CANCER

T-DM1 protects against invasive disease

Women with residual disease following neoadjuvant therapy for HER2-positive breast cancer have inferior long-term outcomes. Now, data from the KATHERINE trial, a phase III open-label study, reveal the superiority of the antibody–drug conjugate trastuzumab emtansine (consisting of trastuzumab conjugated to the cytotoxic microtubule inhibitor emtansine; T-DM1) in improving outcomes in this setting.

A total of 1,486 women with nonmetastatic, invasive primary breast cancer with residual disease after neoadjuvant taxane-based chemotherapy plus trastuzumab followed by surgery were randomly assigned (1:1) to receive 14 cycles, consisting of 3-weekly intravenous doses of adjuvant T-DM1 or trastuzumab. The primary end point was invasive disease-free survival (DFS).

After a median follow-up duration of >40 months in both groups, patients who received T-DM1 had a 3-year invasive DFS of 88.3% versus 77.0% in the trastuzumab group (HR 0.50, 95% CI 0.39–0.64; $P < 0.001$). No significant differences in overall survival were observed at this time point, although more deaths were observed among women in the trastuzumab arm (HR 0.70; 95% CI 0.47–1.05). The benefits of T-DM1 were preserved across all subgroups, including those defined by oestrogen receptor (ER) status.

Fewer women in the T-DM1 arm (71.4% versus 81.0%) completed all 14 cycles of therapy, which reflects a greater risk of grade ≥3 adverse events in this arm (25.7% versus 15.4%). The most common grade ≥3 adverse events in the T-DM1 group included reduced platelet counts (in 3.6% of patients) and peripheral sensory neuropathy (in 1.4%).

In summary, these data support the use of T-DM1 in women with residual breast cancer, owing to their higher risk of disease recurrence. Mature overall survival data from this study are eagerly awaited. The greater risk of adverse events with T-DM1 relative to trastuzumab necessitates good patient counselling about the balance between risks and benefits.

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ORIGINAL ARTICLE von Minckwitz, G. et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1814017 (2018)

PANCREATIC CANCER

FOLFIRINOX goes adjuvant

Owing to a 5-year survival of only ~10% after surgery, the standard-of-care treatment for patients with resectable pancreatic ductal adenocarcinoma (PDAC) involves adjuvant chemotherapy with gemcitabine or a fluoropyrimidine. Fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX), a regimen associated with better outcomes than gemcitabine in the metastatic setting, has now been associated with favourable survival outcomes in the adjuvant setting.

In a phase III trial, patients with resected PDAC and no evidence of metastatic disease were randomly allocated to treatment with modified FOLFIRINOX ($n = 247$) or gemcitabine ($n = 246$). The median disease-free survival duration was longer with FOLFIRINOX than with gemcitabine (21.6 months versus 12.8 months; $P < 0.001$). Subgroup analyses revealed significant benefits with FOLFIRINOX across all patient subsets, except that comprising patients older than 70 years (20.5% of the trial population).

The superiority of FOLFIRINOX over gemcitabine was also observed in comparisons of overall survival (OS; median duration of 54.4 months versus 35.0 months; $P = 0.003$). Of note, median OS with gemcitabine was longer in this trial than in other trials of adjuvant gemcitabine (20.1–26.5 months). This finding might be related to the high percentage of patients in the gemcitabine group (76%) that crossed over to receive FOLFIRINOX after disease relapse.

Grade 3–4 adverse events (AEs) were reported in 75.9% and 52.9% of patients in the FOLFIRINOX and gemcitabine groups, respectively; most of these toxicities were manageable. The regimens differed in their toxicity profiles — among the differences, grade 3–4 diarrhoea affected 18.6% of patients treated with FOLFIRINOX versus 3.7% of patients in the gemcitabine group.

The survival outcomes observed in this study favour adjuvant FOLFIRINOX as a new therapeutic option for patients with PDAC. The weight of factors (such as toxicity profiles or patient age) will need to be considered in decision-making processes when this regimen is adopted in routine clinical practice.

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ORIGINAL ARTICLE Conroy, T. et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N. Engl. J. Med.* **379**, 2395–2406 (2018)