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In this issue

Clinical impact of tyrosine kinase inhibitors in lung cancer

Non-small cell lung cancer (NSCLC) makes up 80% of all primary lung tumours, and is the biggest killer cancer in the developed world. For advanced NSCLC, median survival is poor at 7.9 months and current combinational chemotherapy is associated with high toxicity. Recently, novel drugs against specific molecular targets in NSCLC have been developed and licensed including tyrosine kinase inhibitors (TKI) and monoclonal antibodies to epidermal growth factor receptor (EGFR). The EGFR family is one of the receptor tyrosine kinase (TK) systems involved in cellular signalling and affects proliferation, angiogenesis and cancer cell survival. Currently, two TKIs are in clinical use, gefitinib and erlotinib. These small-molecule agents compete with and prevent the binding of adenosine triphosphate (ATP) to the ATP-binding region of EGFR to prevent tyrosine kinase activity and down stream signalling. However, it has become apparent that only a subset of NSCLC patients responds to gefitinib or erlotinib and those who do, are more likely to harbour EGFR mutations in its TK domain. In the last 12 months, publication of studies correlating *EGFR* gene mutations to clinicopathological features and NSCLC sensitivity to TK inhibition has proliferated. In this issue of *EJC*, Chan and colleagues provide a timely review and capitulation of data from 15 such studies to discuss the impact of TKI in this rapidly expanding field.

Urothelial cancer therapy: an EORTC update

Systemic chemotherapy is the only modality that has been shown in phase III trials to improve survival in advanced bladder cancer patients. In 1985, the M-VAC (methotrexate, vinblatine, adriamycin and cisplatin) regimen showed that urothelial carcinoma was sensitive to chemotherapy. In an attempt to improve results with M-VAC chemotherapy, EORTC protocol 30924 was established to conduct a randomised phase III trial (1996–1998) of high-dose intensity chemotherapy with M-VAC plus granulocyte colony stimulating factor (HD-M-VAC) for comparison with classic M-VAC in advanced transitional cell cancer (TCC). The primary trial objective was to demonstrate an improvement in survival with HD-M-VAC. In this issue of *EJC*, Sternberg and colleagues presents a trial update with a median follow-up in both groups of 7.3 years. The 5-year survival rate for the 263 participants was 21.8% (HD-M-VAC) vs. 13.5% (M-VAC). Median survival was 15.1 months on HD-MVAC and 14.9 months on M-VAC regimen. There was one death from toxicity in each arm; and more patients died of malignant disease in the M-VAC arm (76%) than in the HD-M-VAC arm (64.9%). With longer follow-up, initial results have been confirmed and show that HD-M-VAC produces borderline statistically significant relative reduction in the risk of progression and death compared to M-VAC in TCC.

Co-expression of growth factor and receptor in colorectal cancer

The vascular endothelial growth factor (VEGF) family is important for the process of angiogenesis and tumour growth. The VEGF family exerts its effects through activation of one or more of three related VEGF tyrosine kinase receptors (VEGFRs). The principal lineage that expresses VEGFRs is the endothelial cell, but increasingly receptors are shown to be expressed by malignant cell types, both by human cancer cell lines and tissues. Co-expression of functional VEGFRs with their corresponding ligands in tumours raises the possibility of autocrine loops that can stimulate its growth, progression and survival. This hypothesis also has obvious implications for future therapies. In this issue of *EJC*, Duff and colleagues have aimed to define the expression of different VEGF family members and the VEGFR2 receptor in primary and metastatic sites in colorectal cancer. Thirty colorectal cancers, 12 lymph node metastases and nine liver metastases were immunostained for VEGF-A, VEGF-C, VEGF-D and receptor VEGFR2. The authors conclude that clinical benefit from anti-VEGF antibodies might be increased by directing additional therapies against VEGF-C or against cognate kinase receptors. They go on to suggest that VEGF inhibitors may have both anti-tumour and anti-angiogenic effect in colorectal cancer and also that dual-lineage targets could be critical for the development of effective signal transduction inhibition therapies.

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