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The ERB-B family of receptor tyrosine kinases: Their role in cancer development and as targets for therapy

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The ErbB or EGFR family has four members· EGFR/ErbBl, ErbB2, ErbB3 and ErbB4. The four receptor tyrosine kinases are widely expressed in epithelial, mesenchymal and neuronal tissues and play fundamental roles during development. In addition, EGFR and ErbB2 have been implicated in the development of many human cancers. Regulation of the ErbB receptor function is complex since a large family of ligands, the EGF-related peptides, have been described. By binding the extracellular domain of the receptors, EGF-related peptides induce not only receptor homodimers but also heterodimers. Consequently, although none of these peptides directly bind ErbB2, all of them induce its activation by triggering heterodimerization and cross phosphorylation on tyrosine. By means of intracellular expression of an endoplasmic reticulum (ER) targeted single-chain antibody (scFv) that leads to the specific and stable loss of cell surface ErbB2, we have shown that ErbB2 enhances ligand induced phosphorylation of EGFR, ErbB3 and ErbB4. ErbB2 also potentiates and prolongs the activity of signal transduction pathways stimulated by the EGF-related ligands. These results show that ErbB2 plays a central role in the ErbB family and help explain its potent transforming potential. Intracellularly expressed scFvs have been quite useful for unraveling the complex ligand-induced activation of the ErbB receptor family. In addition we have found that ErbB2 and EGFR-directed scFvs revert cellular transformation induced by the respective receptors.

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Current position of cytokines in the clinical onology of solid tumours

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Cytokines represent the principle (immuno-)therapy of selected solid tumours and are used in the supportive treatment of myelosuppressive chemotherapy. Cytokines (interferons [IFN], Interleukins [IL], tumour necrosis factor [TNF], erythropoietin [EP], G-CSF, GM-CSF, Thrombopoietin [TP]) act as extracellular messengers requiring cytokine receptors (CR) on the target cell. Different cytokines produce similar effects on the immune system: proliferation of the T (and B cells), of natural killer cells (NK) and of macrophagic release of other cytokines. In addition, some cytokines lead to cell differentiation and have anti-angiogenic effects. In renal cell carcinoma (RCC) and malignant melanoma (MM) cytokine treatment has led to response rates from 10–15% (IFN) to 20–40% (IFN/IL-2 ± cytostatics) with a few long-term responders and possible cures. Carcinoid and colonic cancer are other IFN-sensitive malignancies, partly due to synergisim between IFN and 5-FU. Adoptive immunotherapy with LAK or TIL has not resulted in superior results. Adjuvant cytokine therapy in MM and RCC is currently investigated in randomised trials. Isolated limb infusions with TNF and intralesional or intraperitoneal cytokine application have achieved favourable results. The risk of severe side effects during cytokine treatment of solid tumours and high treatment expenses are not negligible. EP, TP, G-CSF, GM-CSF and IL-3 stimulate hematopoetic progenitor cells and may facilitate high-dose chemotherapy of solid tumours.

Conclusion: Cytokine treatment is a valid treatment option in selected patients particularly with RCC and MM. Such treatment should preferably be given as a part of a clinical trial. Cytokines may facilitate high-dose chemotherapy by reducing the risk of myelosuppression and severe febrile events.

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Stereotactic radiotherapy for brain tumours-fact & fiction

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Stereotactic radiotherapy (SRT) is a high precision technique of external beam radiotherapy (RT) The advantage over conventional RT in reducing the volume of normal brain irradiated is seen only for small lesions. The majority of intracranial tumours are large and non-spherical and the best approach is with stereotactically guided conformal radiotherapy (SCRT).

Single fraction SRT/radiosurgery (RS) is a well tolerated alternative to surgical excision in the treatment of solitary brain metastasis. Fractionated SRT/SCRT is a non-invasive alternative to interstitial RT in the treatment of high grade gliomas. The 5 yr PPS of acoustic neuroma treated with RS is 90% with significant toxicity to V, VII and VIII nerves. Use of single fraction SRT in the treatment of benign tumours such as pituitary adenoma, craniopharyngioma and meningioma carries a significant risk of damage, without demonstrable benefit in tumour control compared to fractionated RT. Fractionated SCRT is a potentially less toxic alternative to fractionated RT in the treatment of non-invasive brain tumours and in paediatric brain tumours with a clear need to reduce irradiation of normal brain. SRT/SCRT may be of potential benefit in other tumours where local tumour control is the determinant of morbidity and survival.

SRT is a stereotactically guided high precision conformal RT which reduces the amount of irradiated normal tissue. So far there is no proof of survival benefit over conventional RT in the treatment of the majority of primary brain tumours and single fraction or unconventionally fractionated SRT carry a high potential risk of toxicity. The application of SRT/SRCT should be guided by the knowledge of the natural history of individual tumours and before its introduction into full clinical practice should be tested in well designed prospective trials.