Therefore, EGFR signalling in colon cancer is modulated at the level of receptor capacity, receptor heterodimerization, regulation of intracellular tyrosine kinase activity, ligand presentation and by other costimulatory receptor pathways. These mechanisms have to be considered when therapeutic strategies using EGFR-inhibition are evaluated.

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S45. THERAPEUTIC DECISIONS FROM MOLECULAR STAGING IN COLORECTAL CANCER

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Colorectal cancer is one of the most prevalent cancers worldwide. Whereas surgery is the basis of therapy, chemo- and/or radiotherapy are used frequently to reduce local and distant recurrences. Many prognostic factors have been defined, with only the UICC classification being relevant for therapeutic decisions at present. The prognosis for an individual patient, however, still cannot be sufficiently predicted. Therefore, many patients will receive radio-/chemotherapy that do not benefit from this treatment. Other patients might not receive radio-/chemotherapy as they are judged to be at a low risk for recurrence, but will develop recurrent disease. Better prognostic factors are therefore needed, in order to individualize the therapeutic strategy. As recurrences after complete tumor removal are most likely caused by disseminated tumor cells, it seems to be a logical approach to develop methods to detect these cells. Ideally, patients in whom tumor cells can be detected should have a worse prognosis and should therefore benefit from adjuvant therapeutic strategies. The effect of this therapy should then become apparent by a reduced detection rate of disseminated tumor cells. Even though some studies demonstrate a prognostic relevance of disseminated tumor cells, the prognostic relevance of these cells is not generally accepted. Due to the heterogeneity of disseminated tumor cells, demonstration of the mere presence of these cells will most likely not be an adequate basis for therapeutic decisions. Molecular characterization of disseminated tumor cells and/or of the primary tumor might be a more successful approach in this respect. The clinical relevance of molecular staging for therapeutic decisions, however, has still to be proven in well designed clinical trials.

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S46. ANTI-TUMOUR POTENTIAL OF ZOLEDRONIC ACID (Zometa®)

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Bisphosphonates have been used extensively for more than 3 decades to inhibit osteoclastic activity in a variety of benign and malignant diseases characterized by increased bone resorption. Due to the bisphosphonate moiety, these compounds bind avidly to bone mineral and accumulate at sites of active bone turnover. During bone resorption they are released and ingested by osteoclasts via fluid-phase endocytosis. The nitrogen-containing bisphosphonates (N-BPs) inhibit a key intracellular enzyme in the mevalonate pathway, farnesyl pyrophosphate synthase, thereby reducing prenylation of small GTPase signalling proteins that are essential for osteoclast function and survival. Consequently, bone resorption is impaired and osteoclast apoptosis is induced.

Zoledronic acid (Zometa®) is a novel compound which retains the bisphosphonate "bone hook" and possesses a heterocyclic imidazole substituent containing 2 nitrogen atoms. X-ray crystallography studies with human farnesyl pyrophosphate synthase have shown that the zoledronic acid molecule binds with high affinity to the active site of the enzyme and induces an irreversible conformational change that prevents further access of substrate. Structure-activity studies with more than 300 novel compounds identified zoledronic acid as the lead candidate for clinical development due to its outstanding potency as an inhibitor of osteoclastic bone resorption both in vitro and in vivo, and its excellent in vivo tolerability.

In animal models of breast cancer, prostate cancer, osteosarcoma and haematological malignancies such as multiple myeloma and leukaemia, low doses of zoledronic acid markedly inhibit osteoclastic activity and thus reduce tumour-induced osteolysis and hypercalcaemia. Bone is a rich source of growth factors which are released during bone resorption and can stimulate tumour cell proliferation. By inhibiting osteoclastic activity, zoledronic acid reduces the release of tumour growth factors from bone and thus interrupts this stimulatory cycle. Furthermore, the high local concentration of bisphosphonate at an osteolytic site may exert direct cytostatic and apoptotic effects on the tumour cells in a bone metastasis. Extensive in vitro data show that zoledronic acid is cytostatic and pro-apoptotic against a variety of human tumour cell lines. Interestingly, zoledronic acid enhances the efficacy of some cytotoxic drugs in a synergistic manner, especially when the drugs are administered sequentially rather than concomitantly. Apart from these direct effects on tumour cell proliferation and viability, N-BPs also impair the metastatic behaviour of tumour cells and modulate the host's response to neoplastic disease. In vitro, zoledronic acid potently inhibits tumour cell invasion through extracellular matrix, decreases cell adhesion to both mineralized and non-mineralized matrices, and disrupts soft tissue angiogenesis. Preclinical data from a variety of animal tumour models demonstrate that, in vivo, these effects translate into reduced tumour load, increased tumour cell apoptosis, and in some cases delayed disease progression with a corresponding survival benefit. Although these effects have been predominantly observed in models of bone metastases in nude mice, emerging data indicate that zoledronic acid can also inhibit the growth of primary soft tissue tumours in transgenic animals by a mechanism that apparently involves inhibition of angiogenesis and disrupted macrophage function.

Recently, another intriguing facet has been added to the pharmacological profile of the N-BPs. It has been known for many years that these compounds interact with the immune system to produce an acute phase response in a significant proportion of patients, especially when administered intravenously, but the molecular mechanism remained elusive. It is now known that this effect is caused by inhibition of farnesyl pyrophosphate synthase in monocytes, leading to accumulation of upstream metab-