of signal transduction inhibitors which lead to tumor radiosensitization such as the EGFR inhibitor Iressa®, the Ras processing inhibitor FTI L744,832®, is associated with a decrease in the active form of AKT, direct pharmacological inhibition of the PI3K/AKT pathway by LY291002 and wortmanin cause radiosensitization. Therefore, pharmacological targeting of the PI3K/AKT pathway is a promising novel strategy to improve tumor response to ionizing irradiation.

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Modulators of apoptotic signaling

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In order to increase the efficacy of ionizing radiation or to reduce radiation mediated side effects research centers for translational radiation oncology head for a specific modulation of defined cellular death pathways. In this regard, several signaling systems proved to be of high potential value. It has previously been shown that apoptotic pathways induced by ionizing radiation are distinct from pathways triggered by death ligands (e.g.TRAIL). The combination of both was highly efficient in vitro and preclinical mouse models. However, several aspects of normal tissue toxicity have not been solved and no phase I data are available yet. Thus, up to now the use of TRAIL is limited to experimental settings. A second approach which is currently tested in a phase I trial is based on the observation that synthetic phospholipid derivatives strongly enhance apoptotic effects by modulating the balance between the mitogenic, antiapoptotic MAPK and phosphatidylinositol 3'-kinase (PI3K)/Akt, and the proapoptotic JNK signaling pathways. Furthermore, others provided evidence that an inhibition of anti-apoptotic signals by mitogenic signals increases radiation responses. In this context, controversial data are available regarding the influence of a pharmacological abrogation of MEK1, Erk1/2 signaling on apoptosis sensitivity. However, inhibition of the PI3K/Akt survival pathway using compounds like the PKC inhibitor PKC412 was shown to induce apoptosis or to increase the apoptosis sensitivity of tumor cells. Therefore, these drugs may be used alone or in combination with radiation in order to increase tumor control. Several other drugs including COX-2 inhibitors, betulinic acid and proteasome inhibitors were shown to interact with apoptosis signal transduction. Again, most of the drugs have not been tested in combination with radiation in vivo or – in the case of COX-2 inhibitors – exert pleiotropic effects. Although the examples presented above cannot be considered to reflect all available strategies, it becomes clear that several promising approaches targeting defined cell death pathways have been developed and entered clinical trials. The use of synthetic phospholipid derivatives in a phase I trial is one of the first important examples proving that basic research in radiation biology finally guides the development of new treatment strategies. This and other approaches will increase tumor control rates and reduce side effects in the future.

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Molecular determinants of glioma biology

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We have been studying a series of 190 astrocytic gliomas (136 glioblastomas (GB), 39 anaplastic astrocytomas (AA) and 15 astrocytomas (A)) for abnormalities of genes in the RB1 pathway (CDKN2A, CDKN2B, CDK4 and RB1), the p53 pathway (p14ARF, MDM2, and TP53), as well as PTEN and EGFR. A main finding was that 67% of A and AA had no wild-type TP53 or one mutated allele with a wild type allele. These were the main findings A and AA. Only 29% of the GB had no wild type TP53 and an additional 6% had one mutated allele. Loss of wild type p14ARF occurred in 38% of GBs and a further 8% had amplification and overexpression of MDM2. Thus 76% of GB (103/136), 72% of AA (28/39) and 67% of A (10/15) had a deregulated p53 pathway - almost a prerequisite for astrocytic tumors. All A had at least one wild type RB1 gene and no other abnormalities of this pathway. Abnormalities of the RB1 pathway occurred in 21% AA and 67% GB either by mutation/loss/ homozygous deletion of RB1, CDKN2A and CDKN2B, or amplification of CDK4, indicating that disruption of the RB1 pathway is involved in astrocytic tumour progression. Amplification of the EGFR gene was not observed in A, was unusual in AA (8%) but common in GB (33%). Loss of wild type PTEN occurred in one AA (3%) but in 47% of GB. Both EGFR amplification and loss of wild type PTEN were found with all combinations of the other genetic abnormalities. Survival of patients with GB is typically 11 to 12 months. We studied whether any of the genetic factors examined were related to survival in GBs. Abnormalities in any of the four genes (CDKN2A, CDKN2B, RB1, CDK4) coding for components of the Rb1 pathway were associated with shorter survival (p=0.002). When combined with loss of wild-type PTEN the association was stronger (p

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What next in low grade glioma therapy

Abstract not received.

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Does radiotherapy matter?

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Radiotherapy (RT) remains the principal treatment modality in patients with malignant glioma. Conventional treatment to 60 Gy provides median survival benefit of approximately 6 months with no further advantage for higher doses. RT should be tailored to prognosis with radical treatment reserved for favourable prognosis patients; those with adverse prognostic features (defined by age and performance status) should receive palliative treatment. Attempts at improving the results of RT have concentrated on altered dose and fractionation (hyperfractionation and/or acceleration), the use of modifiers of radiation response and particle irradiation. Most have shown little benefit in single arm or randomised studies. High dose localised irradiation in the form of brachytherapy or stereotactic radiosurgery/radiotherapy boost have also failed to demonstrate prolongation of survival while associated with increased toxicity. Present research strategies concentrate on biological methods to overcome tumour hypoxia, on combined chemoradiotherapy approaches and on the use of biological modifiers, which may in association with radiation improve therapeutic ratio. New agents under evaluation include modifiers of EGFR signalling pathway, COX 2 inhibitors, modifiers of Ras signalling pathway and angiogenesis inhibitors. Radiotherapy remains the most effective primary treatment modality in patients with malignant glioma. New approaches to modification of radiotherapy have a real chance to demonstrate improved therapeutic ratio over RT alone. Before introduction into clinical practice they need robust preclinical and clinical testing.

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Current status of malignant glioma chemotherapy - hype or hope?

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Brain tumors are among the most debilitating diseases. Treatment options are limited to surgery and radiation, the role of chemotherapy has been marginal. Nitrosourea-based chemotherapy has shown activity in selected patients, but failed to show a benefit as adjuvant therapy for malignant glioma in a large randomized trial. Higher response rates to PCV-chemotherapy have been demonstrated for oligodendroglioma, in particular when associated with deletions on chromosomes 1p and 19q. Recently temozolomide (TMZ), a novel alkylating agent has been approved. The low response rates of only 5-8% in glioblastoma (higher in anaplastic astrocytoma) and the absence of phase III data have cast doubts whether TMZ offers a clinically relevant benefit over older alkylating agents. Some benefit may simply be derived by the closer follow-up and better supportive care in patients receiving chemotherapy. More intensive TMZ schedules are being explored. Continuous administration of alkylating agents will deplete the cells of the DNA repair enzyme O6-alkyltransferase (AGT), and may thus have a theoretical advantage over the intermittent schedules. No comparative data are available. Combining X-irradiation with TMZ has been shown to be at least additive in vitro in some glioblastoma cell lines. Using chemotherapy with intrinsic activity immediately after diagnosis together with radiotherapy may allow eliminating microscopic infiltrating disease early in the disease course. Concomitant administration of chemoradiotherapy may increase the radiosensitivity. In a phase II trial we treated 64 patients with newly diagnosed glioblastoma multiforme with TMZ and concomitant radiotherapy. At a median follow-up of now over 3 years the median survival of 14.3 mo (95% c.i. 10.4-18.3) and in particular the 2-year survival of 28% (17-39%) are promising for this poor-prognosis group of patients. A large international randomized trial conducted by the EORTC and the NCI Canada has accrued over 550 patients. Conclusive resuts are expected in early 2004. Insights into gene expression and signaling pathways have