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Improved tumor control and absence of late neurotoxicity using alpha (213Bi) as compared to beta (90Y) labelled-DOTA-Substance P for the treatment of low grade gliomas

Low-grade gliomas (LGG) of astrocytic, oligodendrocytic or mixed phenotype represent an unmet medical need as orphan disease. Due to relatively long median survival time of 8-15 years, prospective clinical studies are rarely conducted. Recommended therapeutic regimens range from an observational strategy to extensive resection with awake craniotomy in order to diminish the risk of transformation into a higher grade glioma. We have conducted an observational study in 8 low grade gliomas using the radiopeptidic targeting vector [213Bi]/[90Y]-DOTA-substance over a period of 18 years (4-18 years, median). Besides therapeutic efficacy, we assessed long-term effects, especially late neurotoxicity of beta- and alpha-therapy following local injection. Since biodistribution of the small peptidic vector (1.8 KD) extends over large parts of the ipsi- and possibly contralateral CNS, late toxicity is of principal concern although no NK-1 receptors are expressed in the normal supratentorial brain. The alpha particles releases their decay energy within an ultrashort range that represents the diameter of 1-2 tumor cells (virtual single cell radiotherapy) while beta-therapy targets many more cells (cross-fire effect). We are comparing long-term side effects following alpha-therapy (Bi-213, range 0.1mm) with those of beta-therapy (Y-90: range 5mm, 2.3 MeV). So far, no recurrence or late toxicity has been observed in newly alpha-treated LGG over a period of 18 (OGII), 11 (AII), 10 (AII), 7 (OGII), 4 (OGII) and 3 (AII) years. Injection of [213Bi]-DOTA-substance into an LGG infiltrating the motor cortex was well tolerated with only transient neurological deficits. In contrast, all Y-90 treated LGG cases either developed signs of late radiotoxicity or recurrence after an observation interval of 8-10 years. Two of these beta-cases were subsequently treated with one cycle of alpha-therapy. One of them showed a slight worsening of pre-existing aphasia, presumably due to previous application of high-dose beta irradiation. In conclusion, local alpha therapy appears to be superior to beta-therapy regarding long-term tumor control and late toxicity.

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