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Vectorization of hypoxia activated prodrugs to chondrosarcoma proteoglycans: evaluation and characterization of antitumoral activity

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Introduction: Chondrosarcoma, or malignant cartilage tumor, represent the second most frequent primary malignant bone tumor in adults after osteosarcoma. Due to its abundant chondrogenic extracellular matrix, its poor vascularization and its hypoxic microenvironment, chondrosarcoma is highly resistant to conventional chemo and radio-therapeutic treatments. Today, only effective treatment remains surgical resection. UMR990 Inserm/UDA unit, develops a new innovative therapeutic targeting strategy which exploit the two characteristics of chondrosarcoma microenvironment: a chondrogenic extracellular matrix (ECM) and a hypoxic tissue. Due to the high sulfate and carboxylate groups of the glycosaminoglycan moieties of proteoglycans (PG), the ECM exhibit a high density of negative charges that may interact with the positively charged quaternary ammonium (QA) function. We propose thus, to vectorize, with QA as vectors to PGs of chondrosarcoma, cyclophosphamide derivative hypoxia activated prodrugs with nitroimidazole or nitrofurane as cleavable entity.

Methods: Firstly, QA derivatives of nitroimidazole and nitrofurane were synthesized and evaluated for their cytotoxic activities on human chondrosarcoma HEMC-SS cell line, respectively to their non vectorized equivalents and to a vectorized but non cleavable equivalent, in normoxia (21 % O2) versus hypoxia (0.3 % O2). In a second time, antitumor efficacy was determined on HEMC-SS xenograft model in SCID (Severe Combined ImmunoDeficiency) mice, with tumor volume, anatomopathology and Western-Blot analyses (PCNA and p53). Adverse side effects were also determined by mouse weight and hematological analyses.

Results: QA derivatives of nitroimidazole prodrug evidenced, in vitro, the best hypoxia versus normoxia differential cytotoxic activity (4.5 times more apoptotic cells in hypoxia than in normoxia). In vivo, this molecule demonstrated a very promising antitumor efficiency, with a tumor growth inhibition (TGI) of 62.1% compared to only 8% for its non-vectorized equivalent. Interestingly, hematological side effects were less pronounced for the QA-prodrug respectively to the non vectorized molecule.

Conclusion: These promising results validate the approach of dual selectivity for chondrosarcoma treatment, especially for the nitroimidazole compound, by increasing its therapeutic index. This new innovative therapeutic strategy offer a real hope for treatment of the tumoral pathology of cartilage, relatively rare, but redoubtable.

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