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Chapter 1 : Preclinical and Clinical Modulation of Anticancer Drugs - CRC Press Book

Preclinical and Clinical Modulation of Anticancer Drugs focuses on the theoretical and practical approaches to designing and enacting modulation principles. Each class of anticancer drug and the different types of modulators used within each drug class are discussed within individual chapters.

Received Jul 10; Accepted Nov This article has been cited by other articles in PMC. Abstract Background Standard chemotherapy in unresectable biliary tract carcinoma BTC patients is based on gemcitabine combined with platinum derivatives. However, primary or acquired resistance is inevitable and no second-line chemotherapy is demonstrated to be effective. Thus, there is an urgent need to identify new alternative chemo therapy approaches. Gene expression profiling was also analyzed upon ET treatment in in vivo models. In EGI-1 and patient-derived xenografts, ET induced tumor growth delay and reduction of vasculogenesis. In vivo ET induced a deregulation of genes involved in cell adhesion, stress-related response, and in pathways involved in cholangiocarcinogenesis, such as the IL-6, Sonic Hedgehog and Wnt signaling pathways. Conclusions These results suggest that ET could represent an alternative chemotherapy for BTC treatment and encourage the development of clinical trials in BTC patients resistant to standard chemotherapy. Electronic supplementary material The online version of this article doi: Biliary tract carcinoma, ET, Preclinical model, Chemotherapy, Patient-derived xenograft Background Biliary tract carcinoma BTC is a particularly lethal malignancy arising from the ductal epithelium of the biliary tree, either within the liver or from the extrahepatic bile ducts [1]. Different chemotherapeutic agents have been employed [3]; few randomized trials have established the combination of gemcitabine GEM and platinum compounds to be the standard of therapy for unresectable BTC patients [4 â€” 6]. These studies, therefore, demonstrated that there are very limited possibilities for prolonging survival of BTC patients, and that it is crucial to find novel therapeutic strategies for the treatment of BTC patients. Ecteinascidin ET , a compound isolated from the marine tunicate Ecteinascidia turbinata[7 , 8] with a potent cytotoxic activity against a variety of tumors in vitro and in vivo[9 , 10], has been approved for treatment of soft-tissue sarcoma and ovarian cancer [11 , 12]. Its mechanism of action is linked to binding to the minor groove of DNA and to a variety of modulatory effects on the tumor microenvironment, including changes in the production of several inflammatory mediators like the chemokines CCL2 and CXCL8, the cytokine IL-6 and the angiogenic factor VEGF [13]. Chronic inflammation contributes to cancerogenesis and disease progression in different types of solid tumors [14 , 15]. Tumor-associated macrophages TAMs represent the major class of immune cells within the tumor microenvironment [16] and have been shown to promote tumor proliferation, increase invasiveness and mitigate T cell-mediated cytotoxic antitumor responses [17 â€” 19]. They are regarded as potential targets in anticancer therapies and, in this context, ET may represent a suitable tool to overcome myelomonocytic cell-mediated exacerbation of the malignant phenotype and immune suppression [20]. Literature reports only the anecdotal case of a BTC patient involved in a phase I study who experienced a complete metabolic response with ET [22]. Here, we investigated the potential anti-tumor activity of ET and its effect on gene expression profiling in human preclinical models of BTC. Primary cell cultures were isolated from peritoneal liquid obtained by paracentesis procedure from two patients with ICC. For in vitro experiments, 0. All tests were performed in quadruplicate and repeated in three independent experiments. Three independent experiments were performed. Blots were stained using standard procedures and signals were revealed by a chemiluminescence reagent Euroclone, Milan, Italy. Tumor size was measured weekly. Tumors were formalin-fixed, paraffin-embedded FFPE for immunohistochemical evaluations. The experiment was carried out by two technical replicates. Arrays were scanned and images analyzed by the Feature Extraction Software from Agilent Technologies version Background correction was performed with the normexp method with an offset of 50, and quantile was used for the between-array normalization. The empirical Bayes method was used to compute a moderated t-statistics [27]. The threshold for log FC of 0. Results ET induces cell cycle

perturbation, apoptosis, and activation of proteins involved in DNA damage-repair in biliary tract carcinoma cells in vitro To investigate the capability of ET to interfere with cell growth, BTC cell lines and primary cultures were treated with escalating doses 0. Table S1 [28]. Figure S1, ET caused a different distribution in cell cycle phases. The common evidence was an increment in the subG0 phase cell fraction, particularly evident in the KMCH cells, indicating that the growth inhibition by ET could be mainly due to the induction of apoptotic cell death. We investigated whether ET was capable of activating the complex DNA damage-repair protein machine.