Therapeutic efficacy of brief intraperitoneal radioimmunotherapy of ovarian cancer using 213Bi-anti MISRII antibodies

Abstract:
Hypothesis: We assessed in in vitro and in vivo models of ovarian cancer the therapeutic efficacy of 16F12 mAbs directed against Mullerian Inhibiting Substance type II receptor (MISRII) radiolabeled with 213Bi. Methods: In vitro, both direct and bystander cytotoxic effects were measured using clonogenic assay and standard medium transfer protocol. Typically, Clonogenic survival was assessed in SK-OV-3 donor cells expressing MISRII and exposed for 90 min to 0.06-0.5MBq/mL of 16F12 213Bi-mAbs. Bystander cytotoxicity was measured in recipient cells grown in non-radioactive culture medium preconditioned for 2 hours in the presence of donor cells. DNA double strand breaks (DSBs) were measured in both donor and recipients cells using immunofluorescent detection of gamma-H2AX and of 53BP1. In vivo we explored in athymic nude mice bearing intraperitoneal (IP) MISRII-expressing AN3CA tumor the therapeutic efficacy of brief-intraperitoneal radioimmunotherapy (BIP-RIT, 12.95 - 37 MBq; 37MBq/mg) or of intraperitoneal RIT (IP-RIT; 2.96-12.95 MBq; 37MBq/mg) using 213Bi-16F12. BIP-RIT mimics hyperthermic intraperitoneal chemotherapy as used in clinic. It consists of intraperitoneal injection of high activities of radiolabeled mAbs followed 30 min later by wash of the peritoneal cavity with saline solution to remove unbound radioactivity. The biodistribution of radiolabeled antibodies following IP-RIT (12.95 MBq; 37MBq/mg) or BIP-RIT (37 MBq; 37MBq/mg) was assessed. Results: In vitro we showed in donor cells a strong direct cytotoxicity of 16F12 213Bi-mAbs. A significant bystander cytotoxicity was also measured in recipient cells. Genotoxic effects were also demonstrated as measured by the formation of DNA DSBs in both donor and recipient cells. In vivo, results of biodistribution indicated that tumour uptake of 213Bi-16F12 during BIP RIT was higher than after IP RIT. The tumour-to-blood uptake ratio was 9 versus 3, respectively, one hour post RIT while it decreased down to 3 and 1, respectively, three hours post-RIT. Finally, a similar delay in tumor growth was observed in mice treated with 12.95 MBq of 213Bi-16F12 following IP-RIT or treated with 37 MBq using BIP-RIT. Conclusions: We confirmed in vitro the therapeutic efficacy of newly developed 16F12 213Bi-mAbs. In vivo results indicate that similar therapeutic efficacy and lower toxicity could be obtained with BIP-RIT compared with IP-RIT. BIP-RIT could be a new tool in the therapy of peritoneal carcinomatosis.

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