Effect of Multidrug Resistance Gene-1(MDR1) Expression on In-Vitro Uptake of Tc-99m sestaMIBI(MIBI) in Murine L1210 Leukemia Cells

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Background: Resistance of malignant tumors to multiple chemotherapeutic agents is a major cause of treatment failure and one of the most important mechanisms of multidrug resistance is an increased expression of plasma membrane P-glycoprotein. P-glycoprotein can recognize and transport a large group of cytotoxic compounds sharing little or no structural or functional similarities, other than being relatively small, hydrophobic and cationic. Recent studies have proved that Tc-99m MIBI is transported by the P-glycoprotein in insect cells with overexpression of recombinant multidrug resistance P-glycoprotein.
Purpose: To demonstrate that Tc-99m MIBI is recognized by the multidrug resistant P-glycoprotein, we have quantitatively measured Tc-99m MIBI uptake in cancer cells with or without expression of MDR1 gene which is responsible for P-glycoprotein. The relationship between Tc-99m MIBI uptake and expression of MDR1 gene was evaluated.
Methods: Multidrug resistance cell lines were induced from murine leukemia cell line(L1210, mouse lymphocytic leukemia cell, ATCC) with continuous challenging low dose adriamycin (Adr cell) or vincristine (Vcr cell) in culture media. Expression of MDR1 RNA was measured with reverse transcriptase polymerase chain reaction(RT-PCR) using 243 base pair primer (Kizaki et al. Blood 87:725, 1996). Cellular uptake of Tc-99m MIBI was measured at 4°C and 37°C condition, and after incubating for 60-min in 37°C RPMI media with or without 50uM or 200uM verapamil.
Results: RT-PCR of Adr cells revealed an intense band corresponding expression of MDR1 RNA, whereas Vcr cells weaker linear band. In contrast, RT-PCR specimen of L1210 did not show MDR1 band. Incubation of cells with Tc-99m MIBI resulted in higher uptake with L1210 than Adr or Vcr cells in either 4°C (37% L1210 vs 17% Adr or 9% Vcr, $p<0.05$ respectively) or 37°C (48% vs 25% or 23%, $p<0.01$ respectively). In the presence of verapamil, known reverser of PgP functions, incubation with verapamil resulted in increased Tc-99m MIBI uptake in Adr cell line (from 25% to 29% with 50uM or 45% with 200uM) and Vcr cell line(from 23% to 27% with 50uM or 35% with 200uM). Tc-99m MIBI uptake was not changed with verapamil in L1210 cells.
Conclusion: These results demonstrate that MDR1 gene expressing cell lines were effectively induced in in-vitro and Tc-99m MIBI is a transporter substrate recognized by the MDR1 P-glycoprotein. Tc-99m MIBI may be useful for characterizing P-glycoprotein expression in leukemic cells in vitro.