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Original article

Treatment of multidrug-resistant murine leukemia with antisense mdr1 oligodeoxynucleotides

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Summary – To overcome multidrug resistance in a P-glycoprotein-overexpressing P388/ADR murine leukemia cell line, antisense mdr1 phosphorothioate-oligodeoxynucleotide (AS-oligomer) was constructed. AS-oligomer inhibited P-glycoprotein expression and mdr1 mRNA in vitro in a dose-dependent manner, whereas sense mdr1 oligomer (SE-oligomer) had no effect at the doses used. When P388/ADR was treated in vitro with AS-oligomer and doxorubicin (ADR), ADR-resistance was reduced by approximately 2 logs. Furthermore, a single injection of AS-oligomer plus ADR intraperitoneally into B6D2F1 mice with P388/ADR significantly prolonged mean survival time in a dose-dependent fashion. Again, sense mdr1 oligomer had no effect in vivo. No side effects, either acute or chronic, were found with this treatment during the observation period. These results show that antisense mdr1 oligomer could be a useful tool to overcome multidrug resistance.

multidrug resistance / P-glycoprotein / antisense oligodeoxynucleotide / mdr1 gene / leukemia

INTRODUCTION

Multidrug resistance (mdr) genes encode P-glycoprotein (P-gp), an active transporter that pumps cytotoxic drugs out of cells. Thus, its overexpression is associated with anticancer drug resistance [10, 14]. Disrupting P-gp/mdr function might therefore form the basis of a strategy for overcoming the multidrug resistance of cancer cells. Chemosensitizers, differentiating agents, chimeric monoclonal antibody, and antibody-dependent cellular cytotoxicity have been used for this purpose [2, 3, 25]. Another promising approach is to use antisense strategy. Antisense oligonucleotides as sequence-specific inhibitors of messenger ribonucleic acid (mRNA) have been increasingly used in the field of oncogenes, infections, and various growth factors [20]. However, only a few investigators took advantage of antisense (AS) technology to overcome multidrug resistance [17, 23, 24]. These reports showed that, using human cancer cell lines, antisense mdr oligonucleotides inhibited P-gp expression and partial reversal of multidrug resistance. However, it is important to evaluate the amount of mdr1 mRNA following antisense treatment since detection by anti P-gp monoclonal antibody is less sensitive than that of mdr1 mRNA. Furthermore, it has not been reported that antisense mdr oligonucleotides are also effective in multidrug-resistant cancers in vivo. However, P-gp is also expressed in some normal organs [18]. Since murine mdr sequences are different from human ones, investigations using antisense-treated human cancer cells in immunodeficient severe combined immunodeficiency (SCID) mice as in vivo models cannot address this issue. Thus, it is necessary to test, in the animal model, the hypothesis that the AS-oligomer would be useful for overcoming multidrug resistance in vivo without compromising physiological processes of the host. To further address these issues, in vitro and in vivo studies using an animal model were carried out. In our preliminary report, we have shown that antisense treatment in vivo may be feasible in treating multidrug-resistant leukemia [5].

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