

《招待講演》

Radioimmunotherapy Comes to the Clinic

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Although NHL eventually becomes resistant to chemotherapy, it remains responsive to modest doses of external beam radiation used to control local disease. Thus, systemic radioimmunotherapy (RIT) is a logical therapeutic strategy for this multifocal disease. In some instances, the monoclonal antibody alone interferes with processes essential for cell viability. However, in an attempt to improve tumor kill, radionuclides have been conjugated to monoclonal antibodies (MoAbs) for RIT. RIT allows the systemic delivery of radiation targeted by MoAbs to areas of disease while sparing normal tissues.

C2B8 (Rituxan®, IDEC Pharmaceuticals Corporation, San Diego, CA), a chimeric MoAb, is specific for the CD20 antigen. C2B8 has the distinction of being the first MoAb marketed for the treatment of cancer. Anti-CD20 MoAbs react with greater than 95% of B-lymphocytes and greater than 90% of B-cell NHL. C2B8 appears to work by at least two mechanisms: C2B8 enlists immune systems to destroy the cells to which it binds, and C2B8 causes tumor cells to die by apoptosis.

There are two broad approaches to radionuclide dose schedules in RIT. One of these is the administration of a single, large dose of radiolabeled MoAb. The second approach is to divide the total dose of radionuclide into multiple fractions. The rationale for fractionated RIT is based on evidence that the radiation dose to the tumor and the dose tolerated by normal tissues can be increased. Another advantage of fractionating the total radionuclide dose into multiple doses is better distribution of the microscopic radiation dose because of reduced heterogeneity of MoAb targeting over several doses.

A number of potential determinants for the enhanced effectiveness of RIT have been identified of which the most important may be apoptosis. Additionally, continuous low dose rate irradiation may result in cell cycle redistribution with accumulation of cells in G2/M, a highly radiosensitive phase. The interaction of complex factors determines the overall effect of RIT.

In summary, it is apparent that MoAbs can work remarkably well under the right circumstances. One of the most potent ways of augmenting the cytoreductive power of MoAb treatment is to conjugate the MoAb to radionuclides.