123

PRELIMINARY RESULTS OF A PHASE I TRIAL OF ANTISENSE TO BCL-2 IN LYMPHOMA

J. Waters, A Webb, D. Cunningham
Royal Marsden Hospital (RMH), UK

Introdution; It has been well known that T14/18 translocation in follicular lymphoma up-regulates BCL-2, leading to continued expression of BCL-2 protein. Upregulation of BCL-2 leads to extended survivial of the cells and increased chemoresistance. Clinical trials demonstrated correlation between BCL-2 expression and poor clinical prognosis in intermediate and high grade lymphomas. G3139 is an all-phosphorothioate 18mer oligonucleotide targeted to the first six codons of the BCL-2mRNA. It has been shown to specifically down regulate BCL-2 *in vitro* and to have dose dependent activity in mice models of human lymphona as well as other xenograft models of solid tumours. *Methods*; The lymphoma unit at the RMH performed the first phase I trial in all grades NHL pts who relapsed following serveral previous conventional chemotherapy regimens and who expressed BCL-2. Replacing preclinical xenograft model, the patients received G3139 as a continuous, subcutaneous 14 day infusion. The doses were escalated according to EORTC scheme and safety as well as efficacy measured using standard evauation criteria

Results; Until early February 1997, 13 pts were entered in 6 dose escalation cohorts up to a dose of 147.2 mg/m^2/day. Based on excellent systemic tolerance the escalations were made in 100% increments. At the 6th dose level reversible grade 3 thrombocytopenia was observed in 1pt. Mild topical, infusion site irritation which was generally acceptable was seen, but two pts had more severe reversible reactions which were not dose dependent. Blood levels of two pts at the 5th escalation level approximated to the concentration effective in *in vivo* models of lymphoma. Of the first 9 pts, 4pts demonstrated improvement in disease status as defined by clinical and/or laboratory parameters including decrease in BCL-2 protein. One of those 4pts demonstrated minor tumour response. Another patient on the higher dose, who failed 4 prior therapies,with follicular grade II lymphoma, stage IVB, developed complete clinical and radiological response of 30+weeks duration.

Conclusion: We conclude that antisense approach to BCL-2 constitutes a potentially important treatment modality in NHL, leading to responses in poor prognosis patients at doses causing low toxicity. The trial is continuing and the full update will be presented.

124

ANGIOGENESIS-DIRECTED INCORPORATION OF GENETICALLY-MODIFIED ENDOTHELIAL CELLS AS SYSTEMIC ANTI-TUMOR THERAPY.

James A. Zwiebel, Ning Su, Scott Freeman, and John O.Ojeifo
Investigational Drug Branch, National Cancer Institute, Bethesda, MD, Nanjing Railway Medical College, Nanjing, PRC, Tulane Medical Center, New Orleans, LA, and Georgetown University Medical Center, Washington, DC

Our studies have demonstrated the feasibility of an ex vivo, angiogenesis-driven approach to endothelial cell-based gene therapy of invasive tumors. We have have shown previously that genetically-modified endothelial cells (GMECs) administered intravenously (IV) can target and become incorporated into sites of active angiogenesis (Cancer Res. 55:2240, 1995). We have now investigated how well migrating GMECs could take part in neoangiogenesis associated with pulmonary metastases. Following the establishment of tumor metastases, mouse lung endothelial cells (MLECs) that had been transduced with either lacZ, recombinant human interleukin-2 (rhIL-2), of herpes simplex thymidine kinase (HSV-TK) were injected intravenously via the tail vein. Four days following lacZ-MLEC injection, X-gal staining cells were observed within the pulmonary metastases, with the magnitude of X-gal staining increasing during the ensuing days and persisting for at least two weeks. Multiple injections of GMEC resulted in improved targeting and more diffuse X-gal staining of pulmonary metastases. Intravenous injection of MLEC expressing either rhIL-2 or HSV-TK (followed by ganciclovir administration) caused a marked reduction in the size and number of B16F10 pulmonary metastases and prolonged the survival of tumor-bearing animals. These results suggest that (1) IV-administered GMECs can migrate into, proliferate, and survive within the sites of tumor metastasis, and (2) GMEC expressing therapeutic molecules may function as a means of delivering effective anti-tumor therapy to sites of metastatic deposits throughout the body, including clinically undetectable metastases.