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p53-based strategy to reduce hematological toxicity of chemotherapy: A pilot study

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p53 activation is the primary mechanism underlying pathological responses to DNA-damaging agents such as chemotherapy and radiotherapy. Study objectives were to: (1) define the lowest safe dose of arsenic trioxide that blocks p53 activation in patients and (2) assess the potential of LDA to decrease hematological toxicity from chemotherapy. Patients scheduled to receive a minimum of 4 cycles of myelosuppressive chemotherapy were eligible. For objective 1, dose escalation of LDA started at 0.005 mg/kg/day for 3 days. This dose satisfied objective 1 and was administered before chemotherapy cycles 2, 4 and 6 for objective 2. CBC was compared between the cycles with and without LDA pretreatment. p53 level in peripheral lymphocytes was measured on day 1 of each cycle by ELISA essay. Subjects received arsenic at cycles 2, 4 and 6 and no arsenic at cycles 1, 3, and 5. Of a total of 30 evaluable patients, 26 were treated with 3-week cycle regimens and form the base of our analyses. The mean white blood cell, hemoglobin and absolute neutrophil counts were significantly higher in the suppressed group relative to the activated group. These data support the proof of concept that suppression of p53 could lead to protection of normal tissue and bone marrow in patients receiving chemotherapy.

Biography

Joel E Michalek completed his PhD from Wayne State University. He has a broad background in biostatistics pertaining to theory and methods, preclinical and clinical trials, and epidemiology. He has written protocols and grants, analyzed data, and co-authored manuscripts arising from clinical studies in surgery, emergency medicine, cancer, and pediatrics and was formerly Principal Investigator of the Air Force Health Study, a 20-year prospective epidemiological study of veterans who sprayed Agent Orange and other herbicides in Vietnam. He has authored 180 journal articles and two book chapters.

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