ADJUVANT RADIOIMMUNOTHERAPY FOR MICROMETASTASES: A STRATEGY FOR CANCER CURE

Rodney E. Bigler,¹,² Pat B. Zanzonico,¹,² Michaela Cosma² and George Sgouros¹

¹The New York Hospital - Cornell Medical Center
New York, NY, USA

²Memorial Sloan-Kettering Cancer Center
New York, NY, USA

INTRODUCTION

Cancer kills when present methods fail to destroy malignant cells participating in metastatic spread throughout the body. Rarely are current methods successful in controlling these micrometastases once hematologic spread of primary tumor occurs. We have determined by analysis of existing biological and physical data that it is possible to destroy tumor cells including, most importantly, isolated cells distributed within the hematologic system without excessive normal tissue damage using systemically administered radiolabeled antibody. Since the red bone marrow has apertures and a poorly developed basement membrane any plasma-borne antibody rapidly equilibrates with its extracellular space. Direct access of plasma-borne labeled antibody to the tumor cell membrane in the hematologic system is therefore provided. This is not the case for other normal tissues because the capillary basement membrane effectively restricts the entry of radiolabeled antibody into tissue extra-cellular space (half-times - 10 - 50 h), thus effectively minimizing the potential hazard of normal cell surface localization of labeled antibody due to cross-reactivity with normal tissue. Cross-reactivity with any non-hematologic normal tissue for antibodies labeled with short-lived radioisotopes can, therefore, be neglected. Capillary basement membranes in solid tumors, likewise, restrict the rate of antibody entry into the extravascular space of these tissues, therefore, effectively decreasing the amount bound to antigen on tumor cell surfaces. The therapeutic dose-limiting tissue due to the above described accessibility of radiolabeled antibody and to its relatively high radiosensitivity is red marrow. The challenge is to deliver high doses to isolate tumor cells in red marrow and other parts of the hematologic system without excessive red marrow damage. We show by means of simulations using a
mathematical model and microdosimetric calculations what conditions (e.g. isotope, specific activity, administration protocol) can be expected to control cancer by controlling occult metastases when conventional treatment can effectively eliminate primary and large metastatic tumor. Our methods can also, upon request, be used to evaluate the effectiveness of any proposed treatment protocol. Bone marrow aspiration analysis in addition to conventional analyses (quantitative imaging and blood and urine radioassays) will serve not only to allow immediate refinement of any particular clinical trial, but also to validate our predictions.

CURRENT CANCER TREATMENT EXPERIENCE

Cancer is the second leading cause of death in the United States with approximately 420,000 deaths (representing 20 % of total deaths) and 820,000 newly diagnosed cases (representing an incidence of 340 per 100,000 of population) each year (1). Only three forms of cancer: lung, colo-rectal, and prostate in males and lung, colo-rectal and breast in females account for 50 % or more of both total cancer incidence and mortality (1-3). The current age-adjusted five-year survival rate for all neoplasms is 50 % and for lung, colo-rectal, prostate, and breast cancer are 13 %, 50 %, 69 % and 74 %, respectively (2,3). It has recently been reiterated, with much notoriety and general consternation, that overall age-adjusted cancer mortality has actually increased 8 % from 1950 to 1981, with lung cancer mortality increasing over 300 % (3). It was, therefore, concluded that, "...some 35 years of intense effort focused largely on improving treatment must be judged a qualified failure" (3).

While the validity of this assertion may be debated, there is certainly no question that new, more effective strategies for cancer therapy are needed. There is, in particular, a critical need for vastly more effective strategies for systemic therapy: cancer is ultimately fatal when current methods of therapeutic intervention fail to eradicate metastatic cells or micrometastatic tumor deposits (4-7). Indeed, while modern methods of surgery, radiotherapy, and/or regional chemotherapy successfully eradicate the majority of primary tumors as well as regional lymph node metastases the inability to control systemically distributed metastases is the principal reason for the notable lack of progress in reducing cancer mortality over the last several decades (3,7,8). For example, the median time to recurrence subsequent to "curative" tumor resection is less than 12 months for lung cancer, 12 months for colo-rectal cancer, and 18 months for breast cancer (7). Moreover, for all cancers, the five- and ten-year survival rates (2) and the twenty-year survival rate (9) are approximately two-fold and four-fold greater, respectively, for localized versus non-localized cancer. Patients are usually killed by metastases to distant sites carried by the blood stream (hematologic spread). Cancer cells gain access to veins either directly by local invasion (diapedesis or destruction of the capillary endothelium and basement membrane) or indirectly via the lymphatics to the thoracic