Chapter 13

Total Lymphoid Irradiation in Multiple Sclerosis

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Introduction

Immunosuppressive drugs have been increasingly used in both uncontrolled and controlled studies in an attempt to modify the relentless deterioration in neurologic function which commonly occurs in patients with chronic/progressive multiple sclerosis (CPMS) (The Multiple Sclerosis Study Group 1990; Rudge et al. 1989; Hauser et al. 1983; British and Dutch Multiple Sclerosis Azathioprine Trial Group 1988; Ellison et al. 1988). Unfortunately, no unequivocal long-term clinical benefits have been documented with immunosuppressive drugs in carefully controlled trials of CPMS. Further, many immunosuppressive drugs must be given at frequent intervals or even daily to sustain remissions in autoimmune disorders, which obviously increases their potential for toxic side effects including infection and neoplasia.

An alternative method for effective immunosuppression is total lymphoid irradiation (TLI). TLI produces sustained suppression of the immune response, prolongs organ transplant survival, and can induce long-term remissions in both natural and experimental autoimmune disorders (Slavin et al. 1977; Kotzin and Strober 1979; Kotzin et al. 1981; Tanay et al. 1987; Trentham et al. 1981; Strober et al. 1987). TLI has been extensively utilized as a primary therapeutic modality in Hodgkin’s disease (Kaplan 1980), in which it was associated with a relatively low risk of severe bacterial infections. Unlike some cytotoxic drugs, TLI has not been associated with a high risk of hematologic neoplasias in long-term follow-up of patients with Hodgkin’s disease. For example, in 3000 patients with Hodgkin’s disease, second tumors were no more common than expected by chance alone during a 10-year follow-up period (Calin 1985; Bookman et al. 1988). Because of the safety of TLI in Hodgkin’s disease and the effective as well as protracted immunosuppressive effects of treatment, we have used TLI as a therapeutic modality in patients with CPMS. In this chapter, we will review the mechanisms of immunosuppression with TLI, the effect of TLI in other human autoimmune diseases, and our experience with TLI in CPMS.
Immunosuppressive Effects of Total Lymphoid Irradiation

TLI has profound immunosuppressive effects on humoral and cell-mediated immune responses in man and laboratory animals. In Hodgkin's-disease patients treated with TLI, there was relative T-cell lymphocytopenia and B- and null-cell lymphocytosis (Fuks et al. 1976). There were also dramatic decreases in the number of total CD3+, helper/inducer CD4+ and suppressor/cytotoxic CD8+ T-cells (Lauria et al. 1983). Approximately 6–8 months post-TLI, CD8-reactive T-cells returned to pretreatment levels whereas CD4+ T-lymphocytes remained low for an extended period of time (Fuks et al. 1976). Consequently, the CD4/CD8 T-cell ratio remained markedly reduced for at least 5 years (Lauria et al. 1983). Decreased absolute lymphocyte counts returned to pretreatment levels 2 years post-TLI; however, at this time the percentage of T-cells was only half the pre-TLI value (Fuks et al. 1976).

The cells repopulating the blood after TLI exhibited different phenotypic characteristics from the peripheral blood T-lymphocytes prior to radiotherapy. A large disparity between CD3-staining T-lymphocytes and the sum of CD4+ plus CD8+ T-cells was observed and suggested that repopulating cells were immature, and not CD4+/CD8- or CD4-/CD8+ but presumably either CD4+/CD8+, CD4+/CD3- or CD8+/CD3- (Haas et al. 1984). Two-color immunofluorescence analysis suggested that these lymphocytes were CD4+/CD3- or CD8+/CD3- (Haas et al. 1984). There was also increased CD38 reactivity of lymphocytes after therapy (Haas et al. 1984). No detailed phenotypic analysis of these cells has been performed to confirm their immaturity. The reduction of the pool of circulating lymphocytes was accompanied by impaired in vitro cell-mediated lymphocyte function. T-cell proliferative responses to mitogens, allogeneic cells and soluble antigens were profoundly diminished as was delayed hypersensitivity to dinitrochlorobenzene (Fuks et al. 1976).

In rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients, similar changes in T-lymphocytes occurred in response to TLI (Kotzin et al. 1981; Strober et al. 1987, 1988). There was an increase in percent CD8+ T-cells with only a slight reduction or no change in the number of CD8-bearing lymphocytes (Kotzin et al. 1981, 1983; Trentham et al. 1981). The CD4/CD8 T-cell ratio decreased markedly after therapy. The number of B cells declined in the TLI-treated RA patients (Kotzin et al. 1983). There have been no reports on the effect of TLI on the number of B cells in SLE patients or on the number of NK cells in RA and SLE. However, a detailed sequential monitoring of T-, B- and null-cell subset changes occurring early after TLI and throughout a long-term follow-up period has not been performed.

In animal studies, the most striking effects of TLI are the generation of nonspecific suppressor cells capable of abrogating both cellular and humoral immune responses and of inducing tolerance. Antigen nonspecific suppressors of the mixed lymphocyte response (MLR) are large, mononuclear cells, lacking surface markers of mature lymphocytes and are found in the absence of antigenic challenge (King et al. 1981; Okada and Strober 1982a; Oseroff et al. 1984). These “null” cells and neonatal suppressor cells have been called natural suppressor (NS) cells. NS cells are found transiently and can no longer