SHOULD MS BE TREATED BY ESCALATION OR INDUCTION THERAPY? INDUCTION

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Inflammatory activity dominates the early relapsing-remitting stages of MS, while the progressive phase of the disease is characterized by sustained neurodegeneration. However, axonal damage and neuronal loss are evident in the earliest stages of the disease and are related, at least partially, to inflammation. Recommendations for early treatment in multiple sclerosis (MS) are aimed at preventing irreversible axonal damage which may lead to progressive physical and mental disability. The available first line immunomodulators for relapsing MS (interferons and glatiramer acetate, GA) are, however, only partially effective, and most patients will experience disease activity and progression despite being adequately treated. The variability in disease pathology, course, severity and response to immunomodulatory therapies among patients and even within the same patient, along with the complexity and heterogeneity of MS make it unlikely for a single agent to be effective in all patients during all stages of the disease. Several clinical features and MRI parameters early in the course of the disease may predict rapid progression of the disease or poor prognosis. These include male gender, older (>40 years) age of onset, Afro-American or Asian origin, high relapse rate in the first years, incomplete recovery and persistent disability after the first attack, short time to reach EDSS level of 4 or disability at 5 years, severe first attack, cerebellar, pyramidal or sphincter presentation, multifocal presentation, short interval between initial attacks, high MRI T2 lesions number and burden, and MRI gadolinium enhancement.

The current escalation approach in MS may leave patients who are at high risk with suboptimal disease control for several years before treatment is advanced to more potent agents. This may lead to “missing the train” of preventing the accumulation of irreversible damage and permanent disability. For these patients, the strategy of induction therapy may ensure a better and faster control of the disease from the beginning, before more significant damage has occurred. Another instance where induction therapy should be considered is when the patient presents at a later stage of his disease where some damage has already occurred and first-line are less likely to be effective. Induction therapy involves short-term use of an immunosuppressive therapy followed by long-term maintenance therapy with an immunomodulatory drug. In this strategy, potent immunosuppressive drugs are used right from the beginning to exert powerful anti-inflammatory effect and tackle the disease process hard and early. This might “reset” the immune system to prevent epitope spreading and control inflammatory disease activity more effectively than immune modulation, thus preventing early structural damage, controlling disease progression and better preserving brain function. Once disease control is achieved, treatment is switched to maintenance therapy with a better tolerated immunomodulatory drug. The short exposure to the immunosuppressive drugs might ensure that their toxicity (bone marrow suppression, infections, amenorrhea, cardio-toxicity, secondary malignancy, etc.) will be minimized. When the appropriate patients are selected for induction therapy, the benefits may outweigh the risks.

Induction therapy strategy has been successfully used in other autoimmune, infectious and malignant diseases. In MS, induction therapy has been studied using mainly mitoxantrone, with natalizumab and cyclophosphamide being additional options. In 2006, Ramtahal et al. reported their experience with 27 very active relapsing-remitting (RR) MS patients who were treated with mitoxantrone for 5-28 months followed by long-term maintenance treatment with GA after achieving clinical stabilization. A sustained 90% reduction in annualized relapse rate ($p<0.001$) has been observed and disability stabilized or improved in all patients. No gadolinium (Gd)-enhancing MRI lesions were detected in 9/10 patients a mean of 27 months after withdrawal of mitoxantrone. A better standardized regimen has been investigated by Vollmer et al in a randomized study: Forty relapsing MS patients with Gd-enhancing lesions on MRI received either GA alone for 15 months, or 3 monthly mitoxantrone infusions followed by GA for another 12 months. The short-term induction with mitoxantrone was safe and reduced relapse rate by 50% and Gd-enhancement by 70-89% compared to GA treatment alone. Other MRI parameters (change in T2w lesion volume, T1w hypointense lesion volume and proportion of Gd enhancing lesions that evolved into black holes) also favored the mitoxantrone-GA combination. Importantly, there were no unexpected safety issues. Excellent and long-lasting results have also been reported by Le-Page et al who treated 100 aggressive RRMS patients with 6 monthly infusions of mitoxantrone and methylprednisolone, followed by various maintenance therapies in most of the patients. Younger age and lower EDSS were predictors of better response to treatment, supporting the theme of introducing this type of treatment as early as possible in the course of disease. The importance of early immunosuppressive induction therapy was highlighted in another retrospective study by Zaffaroni et al, where a regimen of mitoxantrone followed by interferon beta (IFNβ) was very effective in active clinically isolated syndrome of RRMS, while mitoxantrone was ineffective as rescue therapy in active secondary-progressive MS patients who failed IFNβ therapy. In a French-Italian 3-year randomized trial in 109 aggressive RRMS patients, induction with monthly mitoxantrone and methylprednisolone (MP) for 6 months and maintenance therapy with IFNβ-1b given for the last 27 months was superior to IFNβ-1b

treatment for 3 years combined with monthly MP for the first 6 months: Sustained progression was delayed by 18 months ($p<0.012$), disability at 3 years was reduced by 65%, relapse rate was reduced by 61.7% and MRI activity was reduced in the induction therapy group compared with the IFNβ-1b group. In these induction therapy trials, mitoxantrone was generally well tolerated.

In a recent study, induction therapy with a single high dose of cyclophosphamide followed by long term maintenance with GA in RRMS patients was safe and well tolerated, and appeared to be efficacious in reducing the risk of relapse, disability progression, and new MRI lesions.

Induction therapy may have some drawbacks, such as serious adverse events, suppression of protective autoimmunity and inhibition of remyelination. The short-term use of the potent immunosuppressant and appropriate patient selection may reduce the risks and increase the benefits of induction therapy in MS. While escalation therapy is the evidence for previous treatment failure and its deleterious effects on the patient, induction therapy reduces the probability of treatment failure, changes the early events that determine disease progression and provides a better long-term outcome and prognosis.