Therapeutic poisoning: use of immune suppressive therapy in neurologic diseases

Envenenamiento terapéutico: empleo de terapia inmunosupresora represiva en enfermedades neurológicas

Camilo E. Fadul

RESUMEN

Los quimioterápicos azatioprina y mitoxantrone (MITOX) se utilizan rutinariamente en pacientes con esclerosis múltiple. La azatioprina se usa en el tratamiento a largo plazo de la miastenia gravis (MG). El mitoxantrone se utiliza para el manejo de la esclerosis múltiple y el rituximab, un anticuerpo quimérico monoclonal que agota las células B, se ha utilizado en algunas enfermedades neurológicas autoinmunes y su eficacia es está examinando en varios ensayos clínicos. Esta revisión describe los beneficios y los efectos secundarios de la azatioprina, el MITOX y el rituximab.

La azatioprina reduce la tasa de recaídas en la esclerosis múltiple (EM), hasta en 21 por ciento con un NNT de 7 a10 tratamientos en prevenir una recaída en el primer año, la tasa de recaídas a dos años también disminuye. Como la azatioprina tiene menos efectos secundario que los esteroides, se ha recomendado como un "ahorrador de esteroides " en el manejo a largo plazo de la MG. Sus efectos adversos parecen ser menos prominente en la MG que en la EM porque se utiliza con frecuencia en combinación con esteroides. Los efectos adversos más comunes son gastrointestinales y hematológicos (mielosupresión). Un efecto adverso raro pero grave es el mayor riesgo a largo plazo de malignidad.

El mitoxantrone se aprobó para el manejo de la esclerosis múltiple secundaria progresiva, y de las crisis en la forma de recaídas y remisiones. Varios estudios sugieren que a corto plazo modifica el curso en la resonancia magnética y que estabiliza la neuromielitis óptica. Los efectos secundarios más comunes son alopecia y nausea. Los efectos adversos raros pero graves incluyen la toxicidad cardiaca, que puede tener como resultado insuficiencia cardiaca congestiva. El rituximab es efectivo en las neuropatías asociadas con autoanticuerpos IgM; en la esclerosis múltiple secundaria progresiva y en pacientes con recaída mielitis. También se ha utilizado en el tratamiento de los síndromes neurológicos paraneoplásicos y en MG. El perfil de la seguridad de rituximab requiere estudios adicionales.

Palabras clave: mitoxantrone, azatioprina, esclerosis múltiple.

(Fadul CE. Envenenamiento terapéutico: empleo de terapia inmune represiva en enfermedades neurológicaso. Acta Neurol Colomb 2007;23:156-160).

.

SUMMARY

The chemotherapy agents like azathioprine and mitoxantrone (MITOX) are utilized in a routinely way in patients with multiple sclerosis. The azathioprine is used in the long-term treatment of myasthenia gravis (MG). The mitoxantrone is utilized for the management of the multiple sclerosis and the rituximab, a chimerical antibody monoclonal that exhausts the B cells, has been utilized in some autoimmune neurological diseases and its efficacy is now examining in various clinical trials. This review describes the benefits and secondary effects of the azathioprine, MITOX and rituximab.

The azathioprine reduces the rate of relapses in the multiple sclerosis (EM) even in 21 percent, with a NNT of 7 to10 treatments to preventing a relapse in the first year; the rate of relapses in two years also diminishes. As the azathioprine has less secondary effects that the steroids, has been recommended like a "sparring steroids" in long-term management of the MG. Its adverse effects seem to be less prominent in the MG that in the EM because is utilized frequently in combination with steroids. The most common adverse effects are gastrointestinal and hematological (mielosupresion). An adverse but serious and rare effect is the major long-term risk of malignancy.

The mitoxantrone was approved for the management of the progressive secondary multiple sclerosis, and in the crisis of relapses and remissions form. Various studies suggest that short-term modifies the course in the magnetic

Recibido: 30/04/07. Revisado: 10/07/07. Aceptado: 30/07/07.

Camilo E Fadul MD. *Associate Professor. Department of Medicine. (Hematology/Oncology and Neurology). Dartmouth Medical School. Hanover, NH. Director Neuro-oncology program Norris Cotton Cancer Center. Dartmouth-Hitchcock Medical Center. Lebanon, NH*

Correspondencia: Camilo.E.Fadul@Hitchcock.ORG

resonance image and that stabilizes the neuromielitis optica. The most common secondary effects are alopecia and nausea. A serious adverse effect is cardiac toxicity that can result in heart faillure. Rituximab has been used in the treatment of Ig M autoantibodies neuropathy; in progressive secondary multiple sclerosis and in patients with relapse mielitis. Also it has been utilized in the treatment of paraneoplastic neurological syndromes, and in MG. The security profile of rituximab requires additional studies.

KEY WORDS: mitoxantrone, azathioprine, multiple sclerosis.

(Fadul CE. Therapeutic poisoning: use of immune suppressive therapy in neurologic diseases. Acta Neurol Colomb 2007;23:156-160).

INTRODUCTION

Since the immune system has been implicated in the pathogenesis of several neurologic diseases, the use of immune suppressive medications is frequently needed in neurology practice. Chemotherapy agents like azathioprine and mitoxantrone (MITOX) are being used routinely in patients with multiple sclerosis (MS). Azathioprine is frequently considered for the long-term treatment of myasthenia gravis (MG). Rituximab, a monoclonal antibody that depletes B-cells, has been used for immune mediated neurologic diseases and its efficacy is being examined in clinical trials. This review describes the potential benefits and side effects of azathioprine, MITOX and rituximab in neurologic clinical practice.

AZATHIOPRINE

Azathioprine is a mild immune suppressive therapy that has been used in several neurologic diseases especially MS and MG. In the past it was the most frequent immune suppressive drug employed for neurologic disease, but the advent of agents with a better therapeutic ratio has decreased its use.

POTENTIAL BENEFIT OF AZATHIOPRINE

Multiple sclerosis: several randomized, controlled, double-blinded studies suggest that azathioprine can decrease the relapse rate in patients with MS, but a positive effect on disability has not been established (1-3). Overall the number needed to treat (NNT) to prevent a relapse at one year is considered between 7-10, and there is not enough data to be able to calculate the NNT to prevent disease progression (4). Studies comparing the efficacy of azathioprine with IFN and glatiramer are not available. Extrapolating data from the pivotal studies, calculation of the odds ratio of remaining relapse free for drug-treated MS patients compared to placebo was similar for these three drugs (5).

Myasthenia gravis: although azathioprine is frequently used for patients with MG who progress in spite of steroids, most studies evaluating its efficacy have been small, uncontrolled or in combination with steroids (6-8). Since it has fewer side effects than steroids, it has been recommended as a "steroid sparing" therapy for patients in whom steroids need to be tapered or stopped because of side effects. In some cases, it can be used as first line therapy but its use in this situation has been hampered by the delay in onset of effectiveness after starting treatment (8).

POTENTIAL ADVERSE EFFECTS OF AZATHIOPRINE

Frequent adverse effects: the side effects of azathioprine seem to be less prominent in the MG than in the MS population because the drug is frequently used in combination with steroids (9). A potential explanation for the drug intolerance in MS patients is that the disease is frequently associated to genetic polymorphisms of the enzymes involved in the metabolism of azathioprine (10). The most frequent complications of therapy are hematologic (meylosuppresion that might result in infection), gastrointestinal (nausea, anorexia and vomiting) and in a few patients an idiosyncratic flu-like syndrome.

Uncommon but serious adverse effects: there is the concern that azathioprine therapy increases the long-term risk of malignancy.

Several studies report a low long-term risk of cancer in MS patients receiving the drug for a few years, but the incidence increases significantly after 10 years of therapy (11, 12). Myelodysplastic syndrome is another life threatening complication reported after long term azathioprine use for multiple sclerosis (13, 14).

MITOXANTRONE

Mitoxantrone (MITOX) is a cytotoxic chemotherapy agent that has been approved by the FDA for the treatment of secondary progressive MS, progressive relapsing MS, or worsening relapsing-remitting MS. Several studies suggest that it could modify the short term clinical and MRI course of MS, although the impact on long term outcomes is uncertain. In addition, a small uncontrolled trial revealed a decrease in the relapse rate and stabilization of neuromyelitis optica when compared to the course before the addition of MITOX (15).

Potential benefit of mitoxantrone

Four randomized clinical trials evaluating the efficacy of MITOX for MS have been published (16-19), but no direct comparison can be made between studies since different MS populations, treatment schedules and primary outcomes were evaluated. Even more these clinical trials do no provide Class I evidence to support a type A recommendation for the use of MITOX in the treatment of MS (20).

Unfortunately, the relevant clinical outcomes, reduction in the progression of disability and relapse rate, are evaluated on the short term (maximum three years) and therefore the impact of MITOX on the long term outcome of the disease is unknown. A phase III trial revealed a 17 per cent absolute risk reduction in Expanded Disability Status Scale (EDSS) deterioration of at least one point at two years when comparing the groups receiving MITOX (12mg/m^2) and placebo every three months for two years (17). The NNT to prevent one patient from having an EDSS progression of at least one point at two years is of six patients. The relapse rate at two years is another surrogate outcome used in MS clinical trials, and in the same study there was a 21 per cent absolute risk reduction in the percentage of patients experiencing relapses resulting in a NNT of five to prevent one patient from having a relapse.

Potential adverse effects of mitoxantrone

Frequent adverse effects: toxicity varies according to the schedule followed for the administration of MITOX, but usually given at a dose of 12 mg/m^2 given every three months the toxicity encountered is of mild severity and reversible with stopping the treatment, decreasing the dose, or using appropriate symptomatic medications. Nausea, alopecia, menstrual cycle disorders and infection were the adverse events more frequently seen in the phase III MS trial (17).

Uncommon but serious adverse effects: cardiac toxicity, which may result in congestive heart failure, is the dose limiting adverse effect for MITOX and the lifetime cumulative dose should not exceed 140 mg/m^2. Its use is contraindicated in patients with a baseline left ventricular ejection fraction (LVEF) of less than 50 per cent. Since cumulative dose is the most significant factor correlating with cardiac toxicity the general recommendation is not to exceed the dose of 100 mg/m^2. Nevertheless, diminished cardiac function might occur early on in the treatment with MITOX and therefore LVEF monitoring should be performed prior to each administration of the drug, in addition to the baseline study.

Therapy related acute leukemia (TRAL) happening after the administration of MITOX, is usually an acute myeloblastic leukemia characterized by a short latency, acute onset and cytogenetic changes (21). Previous exposure to an alkylating chemotherapy agent might be a risk factor for the development of TRAL. No other risk factors have been recognized, and its appearance seems to be independent of the cumulative dose of the drug. It is recommended that patients be followed for at least two years after treatment cessation since it might appear several years later (22).

RITUXIMAB

Rituximab is a human-murine chimeric monoclonal antibody that causes rapid and specific depletion of B cells in the peripheral blood (23). Although it has not been approved for any neurologic indication, its effect over B-cells and the fact that it is generally well tolerated makes it an attractive therapy for auto-immune disorders. There have been anecdotal reports of its effectiveness in immune-mediated neurologic disease and there are ongoing studies that will determine their role in neurology.

POTENTIAL BENEFIT OF RITUXIMAB

Immune-mediated polyneuropathies: rituximab has the potential to be an effective treatment of neuropathies associated with IgM auto-antibodies therapy, since the antibodies have been implicated in the pathogenesis of the neuropathy. Several small preliminary studies have looked at the potential benefit of depleting B-cells in patients with immune-mediated neuropathies that had progressed in spite of other immune suppressive approaches (24-27). Although these reports suggest that rituximab might be effective in some patients with antibody-mediated neuropathy, the results are less promising than originally expected (28).

Multiple sclerosis: in a small study, four patients with progressive relapsing myelitis MS received four weekly IV infusions of rituximab (29). There were no relapses for the six-month duration of the study, and most patients experienced an improvement in ambulation. Recent report in abstract form of a phase II study suggest a 58 per cent relative risk reduction of relapses over 24 weeks in the rituximab-treated arm (14.5per cent) compared to the placebo arm (34.3 per cent). Furthers studies are needed to determine the role of this drug in MS.

Neuromyelitis optica: an open label study examined the use of rituximab in eigth patients with worsening neuromyelitis optica. There was no significant toxicity and there was an apparent reduction in number of exacerbations with EDSS improvement when compared to course prior to treatment (30). These results have to be confirmed in a controlled trial.

Paraneoplastic neurological syndromes: three out of nine patients with paraneoplastic neurological syndromes and positive autoantibodies treated with rituximab had neurologic improvement (31).

Myasthenia gravis: several cases of patients with myasthenia gravis that improved after rituximab treatment have been reported (32, 33). Two cases had muscle-specific receptor tyrosine kinase (MuSK) antibody-positive myasthenia. Again there is the need for controlled clinical trials.

POTENTIAL ADVERSE EFFECTS OF RITUXIMAB

Frequent adverse effects: the safety profile of rituximab when specifically used for neurologic disorders is unknown, although probably better that for oncology patients. Mild to moderate infusion reactions, usually during the first infusion, consisting of fever and chills/rigors is the most frequent side effect associated to rituximab. Other rituximab-related symptoms include nausea, pruritus, asthenia, headache and rash.

Uncommon but serious adverse effects: rituximab can cause a severe infusion reaction that might be fatal, typically during the first infusion. Manifestations of this reaction include hypotension, angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, ventricular fibrillation and cardiogenic shock. A recent report of two patients with systemic lupus erythematosus treated with rituximab who died from progressive multifocal leukoencephalopathy alerts about the possibility of this potentially life threatening complication in patients with non-neoplastic diseases.

REFERENCES

1. Ellison GW, Myers LW, Mickey MR, Graves MC, Tourtellotte WW, Syndulko K, et al. A placebo-controlled, randomized, double-masked, variable dosage, clinical trial of azathioprine with and without methylprednisolone in multiple sclerosis. *Neurology* 1989;39:1018-26.

2. Milanese C, La Mantia L, Salmaggi A, Eoli M. A double blind study on azathioprine efficacy in multiple

sclerosis: final report. *J Neurol* 1993;240:295-8.

3. Goodkin DE, Bailly RC, Teetzen ML, Hertsgaard D, Beatty WW. The efficacy of azathioprine in relapsing-remitting multiple sclerosis. *Neurology* 1991;41:20-5.

4. Bryant J, Clegg A, Milne R. Systematic review of immunomodulatory drugs for the treatment of people with multiple sclerosis: Is there good quality evidence on effectiveness and cost? *J Neurol Neurosurg Psychiatry* 2001;70:574-9.

5. Palace J, Rothwell P. New treatments and azathioprine in multiple sclerosis. *Lancet* 1997;350:261.

6. Study GMGC. A randomised clinical trial comparing prednisone and azathioprine in myasthenia gravis. Results of the second interim analysis. Myasthenia Gravis Clinical Study Group. *J Neurol Neurosurg Psychiatry* 1993;56:1157-63.

7. Bromberg MB, Wald JJ, Forshew DA, Feldman EL, Albers JW. Randomized trial of azathioprine or prednisone for initial immunosuppressive treatment of myasthenia gravis. *J Neurol Sci* 1997;150:59-62.

8. Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. *Neurology* 1998;50:1778-83.

9. Hohlfeld R, Michels M, Heininger K, Besinger U, Toyka KV. Azathioprine toxicity during long-term immunosuppression of generalized myasthenia gravis. *Neurology* 1988;38:258-61.

10. Craner MJ, Zajicek JP. Immunosuppressive treatments in MS--side effects from azathioprine. *J Neurol* 2001;248:625-6.

11. Taylor L, Hughes RA, McPherson K. The risk of cancer from azathioprine as a treatment for multiple sclerosis. *Eur J Neurol* 2004;11:141.

12. Confavreux C, Saddier P, Grimaud J, Moreau T, Adeleine P, Aimard G. Risk of cancer from azathioprine therapy in multiple sclerosis: a case-control study. *Neurology* 1996;46:1607-12.

13. Putzki N, Knipp S, Ramczykowski T, Vago S, Germing U, Diener HC, et al. Secondary myelodysplastic syndrome following long-term treatment with azathioprine in patients with multiple sclerosis. *Mult Scler* 2006;12:363-6.

14. Then Bergh F, Niklas A, Strauss A, von Ahsen N, Niederwieser D, Schwarz J, et al. Rapid progression of Myelodysplastic syndrome to acute myeloid leukemia on sequential azathioprine, IFN-beta and copolymer-1 in a patient with multiple sclerosis. *Acta Haematol* 2006;116:207-10.

15. Weinstock-Guttman B, Ramanathan M, Lincoff N, Napoli SQ, Sharma J, Feichter J, et al. Study of mitoxantrone for the treatment of recurrent neuromyelitis optica (Devic disease). *Arch Neurol* 2006;63:957-63.

16. Millefiorini E, Gasperini C, Pozzilli C, D'Andrea F, Bastianello S, Trojano M, et al. Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol* 1997;244:153-9.

17. Hartung HP, Gonsette R, Konig N, Kwiecinski H, Guseo A, Morrissey SP, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002;360:2018-25.

18. Edan G, Miller D, Clanet M, Confavreux C, Lyon-Caen O, Lubetzki C, et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry* 1997;62:112-8.

19. van de Wyngaert FA, Beguin C, D'Hooghe MB, Dooms G, Lissoir F, Carton H, et al. A double-blind clinical trial of mitoxantrone versus methylprednisolone in relapsing, secondary progressive multiple sclerosis. *Acta Neurol Belg* 2001;101:210-6.

20. Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2003;61(10):1332-8.

21. Voltz R, Starck M, Zingler V, Strupp M, Kolb HJ. Mitoxantrone therapy in multiple sclerosis and acute leukaemia: a case report out of 644 treated patients. *Mult Scler* 2004;10:472-4.

22. Cohen BA, Mikol DD. Mitoxantrone treatment of multiple sclerosis: Safety considerations. *Neurology* 2004;63(12 Suppl 6):S28-32.

23. Rastetter W, Molina A, White CA. Rituximab: expanding role in therapy for lymphomas and autoimmune diseases. *Annu Rev Med* 2004;55:477-503.

24. Levine TD, Pestronk A. IgM antibody-related polyneuropathies: B-cell depletion chemotherapy using Rituximab. *Neurology* 1999;52:1701-4.

25. Pestronk A, Florence J, Miller T, Choksi R, Al-Lozi MT, Levine TD. Treatment of IgM antibody associated polyneuropathies using rituximab. *J Neurol Neurosurg Psychiatry* 2003;74:485-9.

26. Renaud S, Gregor M, Fuhr P, Lorenz D, Deuschl G, Gratwohl A, et al. Rituximab in the treatment of polyneuropathy associated with anti-MAG antibodies. *Muscle Nerve* 2003;27:611-5.

27. Rojas-Garcia R, Gallardo E, de Andres I, de Luna N, Juarez C, Sanchez P, et al. Chronic neuropathy with IgM anti-ganglioside antibodies: lack of long term response to rituximab. *Neurology* 2003;61:1814-6.

28. Nobile-Orazio E. IgM paraproteinaemic neuropathies. *Curr Opin Neurol* 2004;17:599-605.

29. Rizvi SA, Bashir K. Other therapy options and future strategies for treating patients with multiple sclerosis. *Neurology* 2004;63(12 Suppl 6):S47-54.

30. Cree BA, Lamb S, Morgan K, Chen A, Waubant E, Genain C. An open label study of the effects of rituximab in neuromyelitis optica. *Neurology* 2005;64:1270-2.

31. Shams'ili S, de Beukelaar J, Gratama JW, Hooijkaas H, van den Bent M, van 't Veer M, et al. An uncontrolled trial of rituximab for antibody associated paraneoplastic neurological syndromes. *J Neurol* 2006;253:16-20.

32. Thakre M, Inshasi J, Marashi M. Rituximab in refractory MuSK antibody myasthenia gravis. *J Neurol* 2007.

33. Hain B, Jordan K, Deschauer M, Zierz S. Successful treatment of MuSK antibody-positive myasthenia gravis with rituximab. *Muscle Nerve* 2006;33:575-80.