Multiple Sclerosis
Counseling Points™
Enhancing Patient Communication for the MS Nurse

April 2007 Volume 3 Number 1

Immunosuppressive Therapy: What You Need to Know

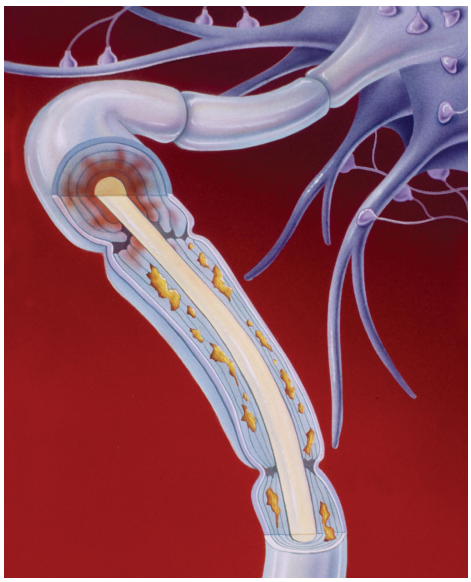
A Roundtable Discussion

Rationale for Immunosuppression

Long-term treatment of multiple sclerosis (MS) originated with the idea of slowing down the immune response. This type of treatment is known as immunosuppression, and several chemotherapy agents have been investigated to combat disease progression. Also known as cytotoxins, these drugs are best known for treating cancers, as they damage or destroy rapidly dividing cells. In MS, the strategy behind immunosuppression is to dampen or modify the immune system's attack on the central nervous system. In contrast, disease-modifying therapies (DMTs) "modulate" the immune system, without actually suppressing it.

The idea of suppressing the immune system can be scary for patients. They assume that after receiving immunosuppressive therapy they will be vulnerable to all sorts of infections. Thus, it is important to emphasize that, in MS, the immune system is overactive or "revved up." Immunosuppressive therapy will "cool off" the immune system, attempting to bring it back to a normal level of activity.

For most patients the term "chemotherapy" conjures up images of hair loss, nausea, and debilitation.



While immunosuppressive or chemotherapy agents can produce a wide range of toxicities, you should reassure patients that the dosing

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Welcome to MS Counseling Points™

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Dear Colleague,

As a multiple sclerosis (MS) nurse, I am sure you are familiar with the disease-modifying therapies (DMTs) available to treat MS. However, some patients may have a suboptimal response to these therapies or their disease may have progressed too far for DMTs to be completely effective. Indeed, DMTs are never completely effective. That's where immunosuppressive drugs come in, medications that have been used in the treatment of MS for more than 30 years. Anecdotally, we know that 15% to 20% of patients are currently receiving some kind of immunosuppressive therapy. This compares with approximately 61% to 80% of patients in North America who are using DMTs, according to the MS International Federation.

In this issue we review some of the immunosuppressive therapies routinely used in MS, such as the FDA-approved cancer agent mitoxantrone. More novel therapies, including stem cell transplantation, are being investigated. As with any treatment, you need to be aware of the potential toxicities associated with immunosuppressive therapies and be prepared to answer the many questions patients will have about their use.

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regimens used in MS rarely lead to complete alopecia and that there are ways to handle other potential side effects, such as nausea and fatigue.

Selecting Patients

There are several circumstances in which immunosuppressive therapies may be initiated. In rare instances, they are used when patients are unable to tolerate DMTs or are diagnosed too late for DMTs to be effective. More often, they are used in patients who continue to progress or worsen despite using a DMT. This phenomenon is described as "suboptimal response," as defined in Table 1.[1] This does not mean that all such patients are candidates for oral or intravenous (IV) immuosuppressive therapy. It is important to keep in mind that the majority of patients with MS respond very well to the DMT injectable therapies and do not require combination regimens. Immunosuppressive drugs are reserved only for those patients who require more aggressive therapy.

Which Agents Are Being Used?

To date, the only FDA-approved immunosuppressive therapy for MS is mitoxantrone (Novantrone®). Other approved immunosuppressive drugs that are not specifically FDA-approved for MS but are often used to treat progressing MS include cyclophosphamide (Cytoxan®), azathioprine (Imuran®), methotrexate (Rheumatrex®), and mycophenolate mofetil (Cellcept®).

Following is information regarding the use of these agents in MS. For practical tips on their administration, refer to the *Counseling Points*™ section on page 8.

Mitoxantrone

The first placebo-controlled, double-blind, randomized, multicenter trial of mitoxantrone's effectiveness in treating MS (the "MIMS" Trial) was published in 2002.[2] This study involved 194 patients with worsening relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) treated with one of two dosages of mitoxantrone (5 mg/m^2 or 12 mg/m^2) every 3 months for 24 months. The mitoxantrone group did significantly better than the placebo group in terms of changes in disability score, ability to walk, number of relapses that required steroid treatment, and the length of time to the first relapse after the start of the study.

For the magnetic resonance imaging (MRI) segment of this study, a subgroup of patients was

Table 1. Criteria for Identifying Patients with Suboptimal Responses to DMTs [1]

Relapses

- Relapse rate of >1/year or failure to show a reduction in relapse rate after continuous therapy with DMTs for ≥6 to 12 months
- Incomplete recovery from repeated attacks, particularly as the EDSS score increases

MRI

- New or recurrent brain stem or spinal cord lesions

Clinical

- Polyregional disease affecting multiple neurological systems
- Progressive motor or cognitive impairment sufficient to disrupt daily activities irrespective of changes on neurological examination, provided the influence of depression, medications, or superimposed concurrent disease is eliminated

DMTs=disease-modifying therapies; EDSS=Expanded Disability Status Scale; MRI=magnetic resonance imaging.

scanned at 12 and 24 months. At 24 months, none of the patients who were treated with the higher dose of mitoxantrone had gadolinium-enhancing lesions compared with 16% of those given placebo. There were also fewer new T_2 lesions in the higher-dose mitoxantrone group than in the placebo group.

On the basis of the results of this and other trials, the FDA approved mitoxantrone for use in patients with progressive relapsing MS, SPMS, and worsening RRMS.

The package insert indicates the maximum lifetime dose for mitoxantrone is 140 mg/m^2.

Mitoxantrone is known to cause heart disease, particularly cardiomyopathy, which may lead to heart failure. It is clear that the risk of heart damage increases with a patient's lifetime dose of mitoxantrone (and the package insert indicates the maximum lifetime dose is 140 mg/m^2).[3] One study found no evidence of heart damage in 20 patients with MS who were given a cumulative dose of 96 mg/m^2.[4] Ghalie et al examined the records from 1,378 patients with MS from three clinical trials to evaluate the danger of heart damage and found that, of these patients, only two (0.15%) developed heart failure after 29 months of follow-up, indicating a fairly low risk of this complication.[5]

Mitoxantrone also has an effect on left ventricular ejection fraction (LVEF). This is the percentage of blood ejected from the left ventricle of the heart during a heartbeat. Of the 1,378 patients in the Ghalie study, 17 patients (1.2%) developed an LVEF <50%.[5] It appeared that a cumulative dose >100 mg/m^2 was associated with an increased risk of decreased LVEF. Unfortunately, this means that while mitoxantrone can be used to stop the progression of MS, it cannot be used over the long term to prevent later progression.

Combining mitoxantrone with a cardioprotective agent may be one option for increasing the safe cumulative lifetime dose. A very small study of seven cancer patients who were given the heart-protective drug dexrazoxane along with mitoxantrone or the related drug daunorubicin found that dexrazoxane permitted the use of fairly high cumulative doses of mitoxantrone or daunorubicin without cardiac damage.[6] At present, the FDA has not approved cardioprotective agents for patients with MS and medical necessity letters are usually required before insurance coverage reimburses for therapy. Thus, more study needs to be done to see if such a strategy might be effective in MS.

Chemotherapy drugs carry with them the risk for developing a secondary cancer, frequently leukemia. Researchers have found it difficult to accurately assess mitoxantrone's contribution to this risk in patients with cancer, because it is usually administered with other chemotherapy agents. In one study of patients with MS who were treated with mitoxantrone, only two of 802 (0.2%) subjects developed leukemia, indicating the risk is quite low.[7]

Another problem that has been experienced with mitoxantrone is transitory or permanent amenorrhea. Women who are planning to have children should be warned of this potential side effect and should consider freezing their ova if they think they may want to have children at a later date. Men are encouraged to consider sperm banking.

The benefits from mitoxantrone treatment are thought to last at least 12 months after the end of treatment. Researchers are looking at a number of strategies to enhance the effects of mitoxantrone in MS:

- combining mitoxantrone with cardioprotective drugs to extend the cumulative dosage;
- combining mitoxantrone with DMTs to enhance efficacy; or
- using mitoxantrone as an "induction" agent, thereby allowing an early and potentially more beneficial effect.

Combining mitoxantrone with DMTs may lead to treatment regimens in which lower doses of mitoxantrone may be used to slow worsening MS, allowing patients to be treated with this agent again when disease progression resumes. It will be interesting to see whether treatment with mitoxantrone allows drugs such as glatiramer acetate or interferon β to regain their effectiveness in patients who have stopped responding to them before mitoxantrone treatment.

Cyclophosphamide

Cyclophosphamide is a form of chemotherapy usually given to patients with cancer and other autoimmune diseases such as systemic lupus erythematosus. It acts by eradicating B and T cells responsible for disease while sparing the pluripotent blood stem cells.

Cyclophosphamide has been used in MS for many years and researched mostly in uncontrolled studies where it was often, but not always, used to treat primary- or secondary-progressive MS. Possible short-term side effects with high doses are hair loss, nausea, hemorrhagic cystitis, and risk of infection. Possible long-term side effects include sterility, birth defects, and increased risk of cancer (especially bladder cancer).

A study published in 2006 suggests that high-dose cyclophosphamide is effective in silencing MS—treating the most severely affected patients with MS who are resistant to traditional treatment—and that this effect appears to be durable.[8] The trial included 13 patients who had Expanded Disability Status Scale (EDSS) scores of 3.5 or higher, with a median score of 6.5. Patients' quality of life (QOL) was also assessed. Half of the patients experienced disease progression even after receiving large doses of mitoxantrone. In addition, almost all of them were taking a DMT and steroids. With the exception of steroids, patients stopped all therapies 3 weeks before initiation of high-dose cyclophosphamide. They were then hospitalized and received a 4-day infusion of 200 mg/kg of cyclophosphamide per day.

The results showed that not only did cyclophosphamide prevent disease progression in all of the patients, but almost 50% experienced a marked improvement in EDSS scores. Patients also experienced a marked improvement in QOL and the majority experienced a clinically significant reduction in fatigue severity scale scores.

At 15 months' follow-up, all of the patients met the study criteria for disease stabilization, and none met the criteria for disease progression. High-dose cyclophosphamide was extremely well tolerated among all patients.

Nevertheless, the adverse-effect profile of cyclophosphamide is not benign and carries with it the risk for infection, transient dilated cardiomyopathy, and bladder complications (e.g., hemorrhagic cystitis) as well as more minor and transient adverse effects, including hair loss, nausea, and loose stools.

The use of azathioprine as a treatment for MS remains controversial.

Azathioprine

The use of azathioprine as a treatment for MS remains controversial. It is commonly used to treat autoimmune diseases such as rheumatoid arthritis, and as part of chemotherapy for some cancers. Over the past 20 years, azathioprine has been, and continues to be, the subject of numerous clinical trials. The results—using different patient populations, different doses, and different protocols—have been mixed.

A recent study demonstrated that azathioprine given at up to 3 mg/kg daily for 6 months to patients with RRMS is associated with a reduction in existing and new MRI lesions, an effect that persisted for 6 months after treatment.[9] The study also suggested that azathioprine was well tolerated, although some patients experienced lymphopenia, gastric pain,

hyperbilirubinemia, and benign peripheral toxoplasmosis. However, these events were reversible.

Side effects are of particular concern with azathioprine. Severe nausea is a major problem. Other potential side effects include severe anemia or leucopenia, liver damage, and a long-term increased risk of developing cancers such as leukemia or lymphoma.

The decision to use azathioprine is a complicated one, and should be made by the physician and the patient together, after a discussion of the potential risks and benefits.

Methotrexate

Methotrexate is used for the treatment of various neoplasms, particularly central nervous system lymphoma. It is also an anti-inflammatory agent and has been prescribed for the treatment of various autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis.

Further trials are required in both relapsing-remitting and progressive groups to establish the role of oral methotrexate in MS.

A Cochrane review of all randomized, controlled trials of oral methotrexate for MS found only one acceptable trial, which studied 60 participants with progressive MS.[10] A nonsignificant reduction in sustained EDSS progression and number of relapses was reported. Minor side effects were observed but there were no major side effects. Further trials are required in both relapsing-remitting and progressive groups to establish the role of oral methotrexate in MS.

General Tips Regarding Infusion Therapy

Patients with MS are frequently disabled and experience bowel and bladder problems because of their disease. Therefore, it is important that health care professionals responsible for infusion therapy are aware of these problems. Whenever possible, patients with MS who are receiving infusion therapy should be positioned near a bathroom, and staff should be made aware that these patients may need assistance in moving from their bed/chair to the bathroom.

Generally, it is important that the IV line be inserted above the wrist and below the elbow to avoid extravasation. For those who have experienced numerous attempts at IV lines, you may want to consider recommending a peripherally inserted central catheter (PICC) line for short-term infusions of <3 months or a porta catheter for long-term infusion therapy.

You should caution your patients that it is imperative that they alert you should they have any signs or symptoms of infection. These include fever, chills, burning with urination, blood in the urine, persistent cough, and even common cold symptoms. They also should notify you if they experience nausea and vomiting, rashes, or anything out of the ordinary following infusion.

Future Directions

Drugs and therapies under investigation include mofetil (Mycofenloate®) (a drug similar to azathioprine), and tacrolimus, an immunosuppressant used for graft rejection.

Of particular interest is cladribine (Leustatin®), an immunosuppressive drug that initially showed positive results in a 2-year study of patients with progressive MS.[11] After the first year, participants exhibited stable neurological scores and lesion volumes on MRI. In a Phase III study, however, no significant effect on disease progression or attack rate was found.

An oral formulation of cladribine is currently being studied. A Phase II study is evaluating the safety, tolerability, and efficacy of two dose regimens of oral cladribine when added to interferon β-1a via a new formulation of subcutaneous injection (Rebif®) in patients with active disease despite treatment with

interferon. A Phase III study is evaluating cladribine as monotherapy for first-line treatment of relapsing forms of MS.

Although cladribine appears to reduce the volume of gadolinium enhancement in patients with both relapsing and progressive forms of MS, it carries an increased risk of bone marrow suppression, headaches, edema of the feet and legs, and viral infections.

Another strategy currently under scrutiny is autologous hematopoietic stem cell transplantation. This was first studied as a treatment for MS in the late 1990s. Results have been analyzed in both single-center and multicenter trials and collectively in a retrospective study by the European Group for Blood and Marrow Transplantation (EBMT). Of the 85 patients with MS in the EBMT database, 74% were found to be progression-free at 3 years from transplantation, a percentage that is fairly consistent with all transplant studies in MS reported to date.[12] The downside to the approach is that there is significant morbidity and it is quite expensive.

In recent years, research in the field of MS has expanded and we have learned that combining DMTs with IV immunosuppressive medications can enhance efficacy, resulting in significantly improved patient outcomes.

Conclusions

The evolution of treatment for MS has come a long way since the 1990s. We now have FDA-approved self-injecting DMTs that help to reduce disease activity and slow down the progression of disability. In recent years, research in the field of MS has expanded and we have learned that combining DMTs with IV immunosuppressive medications can enhance efficacy, resulting in significantly improved patient outcomes. Combination DMT/IV therapies are ever-increasing in the treatment of MS and with continuing research may represent a suitable therapy choice for many patients.

There is little public information about MS infusion therapy. Due to this lack of information, many patients with MS are uneducated on the subject of common IV MS drug therapies, their benefits, side effects, and risks. This often results in uncertainty and angst. We hope that the information provided in this article will help you to minimize patient fears and anxieties that come from the uncertainty of not knowing what to expect with IV MS medications.

References

1. Cohen BA, Khan O, Jeffery DR, et al. Identifying and treating patients with suboptimal responses. *Neurology.* 2004;63(12 Suppl 6):S33-S40.

2. Hartung HP, Gonsette R, Konig N, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet.* 2002;360:2018-2025.

3. Novantrone product labeling. Accessed 3/30/07 at www.novantrone.com.

4. De Castro S, Cartoni D, Millefiorini E, et al. Noninvasive assessment of mitoxantrone cardiotoxicity in relapsing remitting multiple sclerosis. *J Clin Pharmacol*. 1995;35:627-632.

5. Ghalie RG, Edan G, Laurent M, et al. Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. *Neurology*. 2002;59:909-913.

6. Lemez P, Maresova J. Efficacy of dexrazoxane as a cardioprotective agent in patients receiving mitoxantrone- and daunorubicin-based chemotherapy. *Semin Oncol*. 1998;25(4 Suppl 10):61-65.

7. Brassat D, Recher C, Waubant E, et al. Therapy-related acute myeloblastic leukemia after mitoxantrone treatment in a patient with MS. *Neurology*. 2002;59:954-955.

8. Gladstone DE, Zamkoff KW, Krupp L, et al. High-dose cyclophosphamide for moderate to severe refractory multiple sclerosis. *Arch Neurol.* 2006;63:1388-1393.

9. Massacesi L, Parigi A, Barilaro A, et al. Efficacy of azathioprine on multiple sclerosis new brain lesions evaluated using magnetic resonance imaging. *Arch Neurol*. 2005;62:1843-1847.

10.Gray OM, McDonnell GV, Forbes RB. A systematic review of oral methotrexate for multiple sclerosis. *Mult Scler.* 2006;12:507-510.

11. Beutler E, Sipe JC, Romine JS, et al. The treatment of chronic progressive multiple sclerosis with cladribine. *Proc Natl Acad Sci USA.* 1996;93:1716-1720.

12.Saccardi R, Kozak T, Bocelli-Tyndall C, et al. Autologous stem cell transplantation for progressive multiple sclerosis: update of the European Group for Blood and Marrow Transplantation autoimmune diseases working party database. *Mult Scler.* 2006;12:814-823.

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Immunosuppressive Therapy: What You Need to Know

- Reserve immunosuppressive drugs for patients who require more aggressive therapy.
- Always check prescribing information of proposed immunosuppressive therapies for precautions regarding comorbidities and concomitant medications.
- Reassure patients that the dosing regimens of immunosuppressive therapies used in MS rarely lead to complete alopecia and that there are ways to handle other potential side effects, such as nausea and fatigue.

Mitoxantrone

- Administer at a dose of 12 mg/m^2 in 5- to 15-minute intravenous infusions every 3 months. Administering the dose over 30 minutes helps to reduce the incidence of side effects.
- Do not exceed a cumulative lifetime dose of 140 mg/m^2; careful record-keeping is essential.
- To improve tolerance, patients may be given oral prednisone 10–20 mg and an antiemetic prior to treatment.
- Obtain complete blood counts and liver function tests before each dose and 10 to 14 days after each dose.
- Do not administer mitoxantrone to patients with neutrophil counts that are <1,500 cells/mm^3 or when liver function tests show abnormalities.
- Do not give mitoxantrone during pregnancy. Women of childbearing age should receive a pregnancy test before each treatment, even if they are using birth control.
- Advise patients planning to have children to consult a fertility specialist before commencing therapy.
- Test left ventricular ejection fraction (LVEF) before each treatment.

Note: Disease-modifying therapies (DMTs) may or may not be discontinued during mitoxantrone therapy.

Cyclophosphamide

- Administer 800 mg/kg monthly for 3 months. Anecdotally, the maximum cumulative lifetime dose should not exceed 60 grams, including oral doses.
- Direct patients to drink 2 to 3 liters of water for 2 to 3 days and empty their bladder every 2 hours (except at night) for 2 days following the infusion to prevent hemorrhagic cystitis.
- When possible, administer the detoxifying agent mesna (Mesnex®) prophylactically to help prevent hemorrhagic cystitis.

Azathioprine

- Start at 1 mg/kg mg once daily and increase up to 3-4 mg/kg given in two divided doses daily based on white blood cell counts.
- Titrate dose to maintain a white cell count of less than 2500 cells/mcl of blood (neutrophils should be >1000 to 1500 cells/mcl of blood depending on the results of other blood work).
- Perform liver function and hematological testing routinely.

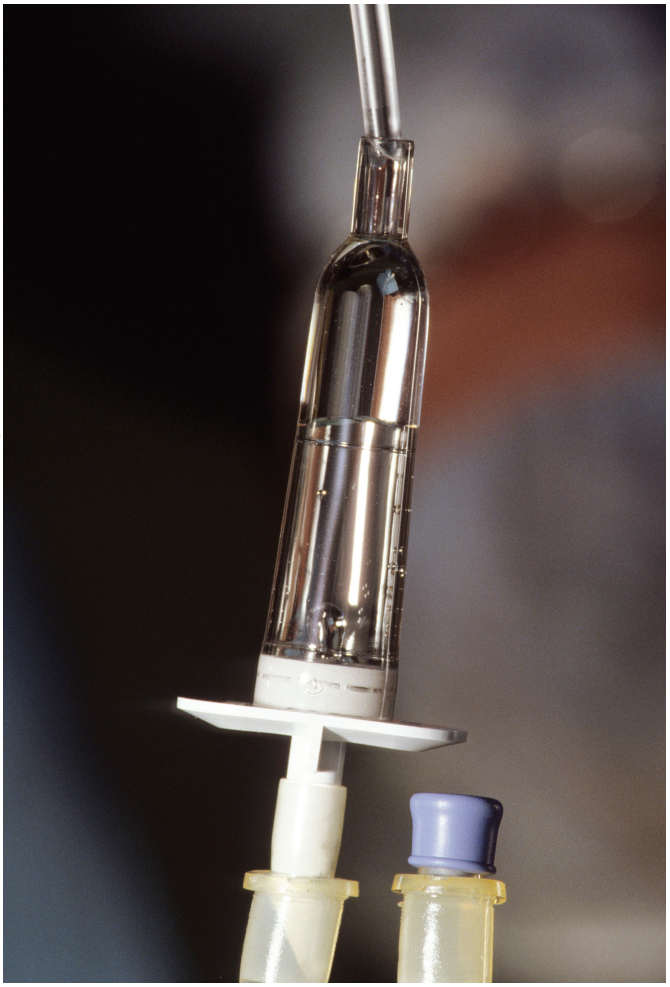
Methotrexate

- Prior to initiating methotrexate, send patients for a chest x-ray to rule out pulmonary fibrosis.
- Dose initially with 2.5 mg tablets, three times per day, and adjust to blood counts.
- Check blood counts every 2 weeks for 2 months and after dosage changes, then every month for 1 year.

In the Literature

Mitoxantrone Combined with DMT Enhances Efficacy

Despite expanding use of emerging therapies (e.g., mitoxantrone, alemtuzumab, and natalizumab) in relapsing-remitting multiple sclerosis (RRMS), trials combining these agents with the disease-modifying therapies (DMTs) glatiramer acetate and the β-interferons remain limited. In an observational series conducted in the United Kingdom, 60 patients were initiated on an induction regimen of 20 mg of mitoxantrone administered once per month for 3 months. The drug was then administered in two further quarterly doses of 10 mg each for a total of 80 mg over 8 months. Glatiramer acetate was initiated in the fifth month, overlapping with mitoxantrone for the final two doses and continuing as maintenance therapy thereafter. So far, data are available on 27 patients followed for between 8 months and 6.5 years. Most were treatment naïve, but six of the 27 patients had previously failed β-interferon therapy, and two had previously failed glatiramer acetate treatment.



To date, only seven relapses have been observed in the entire study cohort. Moreover, disability scores in all patients have remained stable or improved since the beginning of mitoxantrone therapy. Magnetic resonance imaging (MRI) scans of the first 10 patients to undergo this course showed no enhancing lesions and a substantial decrease in overall T_2 lesion load.

Disability scores in all patients have remained stable or improved since the beginning of mitoxantrone therapy.

The author, noting that glatiramer acetate typically reduces the relapse rate by approximately 30%, speculates that the low rate of relapses in this study may be a demonstration of synergy between the two agents. He contrasts his experience with previous studies of mitoxantrone and β-interferons in which disease activity returned rapidly after discontinuation of mitoxantrone. Thus, he urges more study of combination strategies due to the potential for such synergies.

Bogglid M. Rationale and experience with combination therapies in multiple sclerosis. *J Neurol.* 2006;253 [Suppl 6]:VI/45–VI/51.

Mitoxantrone for MS

This article suggests that the indications for the use of mitoxantrone should be refined. The author recommends reserving this agent as a rescue therapy for patients with RRMS with frequent and disabling exacerbations that will possibly lead to permanent, severe disability. He also suggests that mitoxantrone is appropriate for patients in the secondary progressive phase whose Expanded Disability Status Scale (EDSS) scores increase by one or more points per year and who do not respond to DMTs.

Gonsette recommends the following regimen:

- An induction phase with monthly intravenous administration of 12 mg/m^2 for 3 months.
- A maintenance phase with 12 mg/m^2 every 3 months for 2 years, not to exceed the maximum cumulative dose of 140 mg/m^2.

Gonsette notes that cardiotoxicity is clearly dose-dependent and is a strict treatment-duration-limiting factor.

Gonsette RE. Mitoxantrone in progressive multiple sclerosis: when and how to treat? *J Neurol Sci.* 2003;206:203-208.

Myelodysplastic Syndrome Associated with Azathioprine Therapy in Patients with MS

After retrospectively analyzing the complete blood counts of 317 patients with MS treated with azathioprine, Putzki and colleagues found one case of myelodysplastic syndrome in a young patient with MS. This patient had received a cumulative dose of 627 grams. The authors note that four cases of myelodysplastic syndrome after long-term azathioprine therapy in MS have been reported (including their patient). They conclude that these cases suggest a time- and dose-dependent risk, and that patients on long-term therapy with azathioprine require careful monitoring.

Patients on long-term therapy with azathioprine require careful monitoring.

Putzki N, Knipp S, Ramczykowski T, et al. Secondary myelodysplastic syndrome following long-term azathioprine in patients with multiple sclerosis. *Mult Scler.* 2006;12:363-366.

MS Counseling Points™

Immunosuppressive Therapy: What You Need to Know

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