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The use of mitoxantrone in multiple sclerosis treatment

Multiple sclerosis, as an autoimmune disease involving mainly white matter of the brain and the spinal cord, is a very common neurological disorder causing disability in young adults. Clinical patterns of the disease have been identified by international consensus (10). The most common is the relapsing-remitting course of the disease (85%) with relapses and complete or incomplete recovery between them, this pattern is unavoidibly followed by a progressive phase after about 15 years or more (secondary progressive MS), 10% of patients experience progressive course from the onset (primary progressive MS), and the remaining 5% experience progressive disability with superimposed exacerbations (progressive-relapsing MS) (10). For relapsing-remitting course of the disease, there are presently three disease modifying approved therapies : interferon beta-1-b, interferon beta-1-a, and glatiramer acetate. The first registered agent introduced into treatment of secondary progressive multiple sclerosis (SP-MS) in the USA in the year 2000 was mitoxantrone (3).

Mitoxantrone was discovered in 1978 and was previously known as antineoplastic agent used in the treatment of various malignant disorders. It is an inhibitor of both deoxyribonucleic and ribonucleic acids synthesis (1). Presently it is also known as having immunosuppressive and immunomodulatory activity, which can be explained by the fact that mitoxantrone abrogates T helper lymphocytes activity, enhances T suppressor cell function , inhibits B lymphocyte function, diminishes antibodies production and deactivates macrophages (1, 5). The reason for introducing mitoxantrone into multiple sclerosis treatment was its effective suppression of experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis (9).

MOST IMPORTANT TRIALS WITH MITOXANTRONE

Mitoxantrone is the newest immunosuppressive agent, tested among many others in MS treatment in the last years. Most of these agents, such as azathioprine, cyclosporin, cyclophosphamide, sulfasalazine did not turn out to be very useful in multiple sclerosis treatment (4). Since the year 1987, several trials with mitoxantrone suggested its effectiveness in MS with minimal adverse effects. One of the first studies in this field was conducted for 1 year with a dose of mitoxantrone 12 mg/m^2 every 3rd month. Although conducted on a small group of patients (10 patients with secondary progressive course of the disease) and without control group its results suggested effectiveness of mitoxantrone in MS(quotation after 4). After 1-year treatment a decrease in Expanded Disability Status Scale, which allows to measure the level of disability in MS patients (7), as well as the decrease in the number of new gadolinium enhancing T-2 weighted lesions was noticed in the investigated group of patients (quot. after 4). Results of another important study with mitoxantrone in MS were published in 1997 (2). Forty-two patients with SP-MS were included into the study, half of them were given only methylprednisolone and the second half of the patients were given both mitoxantrone 20 mg monthly i.v. and methylprednisolone. (1 g i.v.

monthly). Although the main disadvantage of this study was that it was not a double-blind trial, its results confirmed the results of the previous study. The group treated with mitoxantrone after 1-year treatement, had the lower EDSS score, the greater number of patients without new gadoline enhancing T2-weighted lesions, the lower number of relapses and the lower number of patients with progression of the disease assessed as higher than 1 point in EDSS. Mitoxantrone is an agent causing blue colour of urine and sclerotic coat. That is why it was impossible to carry out a double-blind study in this case.

One of the most important studies with mitoxantrone was a placebo-controlled double blind, randomised, multicenter trial, whose complete results were published in 2002, but the preliminary outcomes were presented in 1998 (the MIMS study) (5). On the basis of this preliminary outcomes and results delivered by Edan's study, in the year 2000 Food and Drug Administration registered mitoxantrone 12 mg/m^2 given intravenously every 3rd month for the treatment of worsening relapsing-remitting, progressive-relapsing and secondary progressive multiple sclerosis (2, 3, 4).

The main aim of the MIMS study was to answer the question if administering mitoxantrone i.v. every third month in a dose of 12 mg/m^2 in RR-MS and SP-MS can be beneficial, especially in the aspect of progress of the disease. Results of the study showed that the patients treated with mitoxantrone experienced benefits compared with placebo group in the following measures: change in EDSS, change in ambulation index (AI-ability to walk 8 meters assessed from 0 to 9 points), change in total number of treated relapses during the 1st and 2nd year after treatment, longer time to the first treated relapse and beneficial change in standardised neurological status. There was also a positive influence of mitoxantrone on neuroimaging, which was in accordance with clinical improvement. Compared with control group significantly fewer patients had enhancing lesions after 2-year treatment. The results of this study were confirmed in another study made by Debouverie in 2004 on 94 patients (1, 5).

When we think about treatment with mitoxantrone, side-effects of such treatment should be also taken into consideration. In all the studies above mentioned mitoxantrone was generally well tolerated; the most frequent side-effects that occurred were: nausea, urinary tract infections, menstrual disorders, amenorrhoea and they were of mild or moderate intensity. Treatment with mitoxantrone is connected with higher risk cardiotoxicity resulting in cardiomyopathy, worsening of the left ventricle ejection fraction and irreversible congestive heart failure (11). This risk is especially high when a cumulative dose of mitoxantrone is higher than 100 mg/m^2. In the MIMS study no patient experienced congestive heart failure, and the difference in the decrease in the left ventricular ejection fraction was not significant between mitoxantrone and placebo groups. Nevertheless, it is suggested not to exceed a cumulative dose of 140 mg/m^2 for the whole therapy.

MITOXANTRONE IN MARBURG VARIANT OF MS

Another interesting use of mitoxantrone in multiple sclerosis can be its use in a severe type of the disease called Marburg Variant. It is a severe monophasic form of MS, leading to advanced disability or even death in a period of weeks or even months (7). No successful treatment of this variant has been described until the last year. A case study of Marburg variant successfully treated with mitoxantrone was presented by Jeffrey in 2004 (6). A 34-year women with the rapidly worsening condition was previously treated with methyloprednisolone 1000 mg i.v. for 5 days without any results. Soon she became stuporous, with no response to verbal commands, she presented a skew deviation, bilateral intranuclear ophthalmoplegia, a right afferent papillary defect, and a right seventh nerve palsy. Multiple sclerosis was confirmed by MRI images and the results of lumbar puncture. At this point she was treated with mitoxantrone 12 mg/m^2 i.v. (20 mg total dose). On the 10th day after MITX treatment the patient became responsive and followed commands. At follow-up 1 year later, she presented no obvious

cognitive deficits, and was fully ambulatory (6). This case study also confirms beneficial effects of MITX in these cases of MS where other therapies turned out to be ineffective.

CONCLUSIONS

Mitoxantrone provides a new therapeutic option for relapsing-remitting patients with frequent exacerbations leading to permanent disability and patients with secondary progressive MS whose disability progression rate increases by one or more points in EDSS per year and who do not respond to other current therapies. Further studies will provide us with exact data on the long-term safety and tolerability of this agent. Taking into consideration present knowledge of side-effects and toxicity of mitoxantrone it should not be used as the first line treatment in relapsing-remitting MS. It should be rather used in advanced phases of the disease, when other immunomodulatory agents turned out to be insufficient or ineffective but we can observe a quick progress of the disease. Its use in MS treatment is limited by its toxicity. Assessment of safety and tolerance of mitoxantrone should be the subject of future research as well as the use of cardioprotective agents that could prolong this useful therapy.

REFERENCES

1. Debouverie M. et al.: Predictive parameters of mitoxantrone effectiveness in the treatment of multiple sclerosis. Mult. Scler., 10, 407, 2004.
2. Edan G. et al.: Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised mulicentre study of active disease using MRI and clinical criteria. J. Neurol. Neurosurg. Psychiatry, 62, 112, 1997.
3. Gonsette R. E.: Mitoxantrone in progressive multiple sclerosis: when and how to treat? J. Neurol. Sci., 206, 203, 2003.
4. Goodin D. S. et al.: Mitoxantrone in multiple sclerosis treatment. Neurology, 61, 1332, 2003.
5. Hartung H. P. et al.: Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet, 360, 2018, 2002.
6. Jefferey D. R. et al.: Treatment of Marburg Variant multiple sclerosis with mitoxantrone. J. Neuroimaging, 14, 58, 2004.
7. Johnson M. D., Lavin P. et al.: Fulminant monophasis multiple sclerosis, Marburg's type. J. Neurol., 53, 918, 1990.
8. Kurtzke J.: Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology, 33, 1444, 1983.
9. Lublin F. D. et al.: Suppression of acute and relapsing experimental and allergic encephalomyelitis with mitoxantrone. Clin. Immunol. Immunopathol., 45, 122, 1987.
10. Lublin F., Reingold S. C.: Defining the clinical course of MS: Results of an internatioal survey. Neurology, 46, 907,1996.
11. Strotmann J. M. et al.: Myocardial function in patients with multiple sclerosis treated with low dose mitoxantrone. Am. J. Cardiol., 89, 1222, 2002.

SUMMARY

Multiple sclerosis, as an autoimmune disease involving mainly white matter of the brain and the spinal cord, is a very common neurological disorder causing disability in young adults. There are four types of the clinical pattern of multiple sclerosis: relapsing-remitting multiple sclerosis (RR-MS), primary

progressive (PP-MS), secondary progressive (SP-MS) and progressive relapsing multiple sclerosis (PR-MS). Presently for relapsing-remitting course of the disease, there are three disease modifying approved therapies: interferon beta-1-b, interferon beta-1-a, and glatiramer acetate. But still there are few therapeutical options for the progressive course of the disease. The first registered agent introduced into the treatment of secondary progressive multiple sclerosis (SP-MS) in the year 2000 was mitoxantrone, which has both immunomodulatory and immunosuppressive activity. The article presents general information on mitoxantrone and the most important trials that have confirmed its effectiveness in secondary progressive multiple sclerosis and in acute type of multiple sclerosis called Marburg variant.

Zastosowanie mitoxantronu w leczeniu stwardnienia rozsianego

Stwardnienie rozsiane jest schorzeniem autoimmunologicznym, związanym z uszkodzeniem głównie istoty białej mózgu i rdzenia kręgowego, a jednocześnie bardzo częstą chorobą neurologiczną, powodującą niesprawność ludzi młodych. Obecnie możemy wyróżnić cztery typy przebiegu klinicznego choroby: postać zaostrzająco-zwalniającą (RR-MS), wtórnie postępującą (SP-MS), pierwotnie postępującą (PP-MS) oraz zaostrzająco-postępującą (PR-MS). Do terapii postaci zaostrzająco-zwalniającej stwardnienia rozsianego są zarejestrowane trzy leki modyfikujące naturalny przebieg choroby: interferon beta 1 a, interferon beta 1 b oraz octan glatirameru. Pierwszym lekiem, który został zarejestrowany w roku 2000 do leczenia postaci wtórnie przewlekle postępującej stwardnienia rozsianego, był mitoxantron. Jest to środek mający działanie zarówno immunomodulujące, jak i immunosupresyjne. Artykuł przedstawia najważniejsze informacje o leku, prezentuje także najistotniejsze próby kliniczne, które potwierdziły skuteczność mitoxantronu w leczeniu SP-MS oraz jego skuteczność w leczeniu gwałtownie przebiegającej postaci choroby, zwanej wariantem Marburg.