CP-087

Evaluation of the safety and efficacy of Mitoxantrone in Cypriot patients with worsening forms of Multiple Sclerosis

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BACKGROUND

Mitoxantrone (MTX) is an antineoplastic agent approved by Food and Drug Administration (FDA) for the treatment of patients with Secondary Progressive (SP), Progressive Relapsing (PR) and worsening Relapsing Remitting (RR) Multiple Sclerosis (MS). No treatment is currently approved for the treatment of patients with Primary Progressive (PP) MS.

PURPOSE

The purpose of our study was to evaluate the safety and efficacy of Mitoxantrone in Cypriot patients with progressive forms of MS.

MATERIALS & METHODS

Patients followed up at a tertiary neurology centre in Cyprus who have been diagnosed with clinically confirmed progressive forms of MS and had either failed or were not candidates for therapy with immunomodulating agents were studied retrospectively for two years.

Patients received 18-20mg of f MTX (12mg/m² of BSA) every 3 months up to a cumulative dose of 140mg-160 mg.

All patients were evaluated by cardiac echo at baseline and every 3 months after introduction of MTX. Mitoxantrone was not administered to patients with Left Ventricular Ejection Fraction (LVEF) less than 50%.

The Expanded Disability Status Scale (EDSS) was applied before treatment and every six months after introduction of Mitoxantrone. Relapses and drug safety were assessed every 3 months unless otherwise required by the patient's disease status.

Statistical analysis was performed using the SPSS v.20 statistical package.

RESULTS

Participants

One hundred and forty-five patients were included in the study. The baseline characteristics of patients at time of Mitoxantrone therapy initiation are shown in Table 1.

TABLE 1: Patient characteristics at time of Mitoxantrone initiation

	Relapsing Remitting N=59 (41%)	Secondary Progressive with Relapses N=13 (9%)	Secondary Progressive w/out Relapses N=34 (23%)	Primary Progressive N=39 (27%)	All patients N=145 (100%)
			N (%)		
Gender (M/F)	29/30 (49%/51%)	6/7 (46%/54%)	10/24* (29%/71%)	24 /15* (61,5%/38,5%)	69/76 (48%/52%)
Patients with previous use of DMT	49** (83%)	13** (100%)	31** (91,2%)	8** (20%)	101 (70%)
			MEAN (STD) / RANGE		
Age of onset of MS	31,2 (9,3) / 15-49	32 (10,3) / 13-54	34,8 (10,3) / 13-54	42,5* (11,5) / 19-70	35 (11,2) / 13-70
Disease duration	10,9 (7,4) / 1-35	15,3 (5,2) / 6-22	15,9 (8) / 5-32	5,4** (4,2) / 1-18	11 (7,7) / 1-35
Annual relapse rate	2,2* (1,2) / 0-6	1,2* (0,8) / 0-3	N/A	N/A	2 (1,2) / 0-6
EDSS Score	5 (1,3) / 1,5-7	5 (1,4) / 3-8	6* (1,6) / 2,5-9	5 (1,4) / 3-8	6 (1,4%) / 1,5-9

*p<0,05
**p<0,001

In between relapsing groups, a significant difference on the mean annual relapse rate was observed (p=0.009) with the patients belonging in the RR MS group experiencing almost twice as many relapses per year compared to patients belonging to the SP with relapse group (Fig.1).

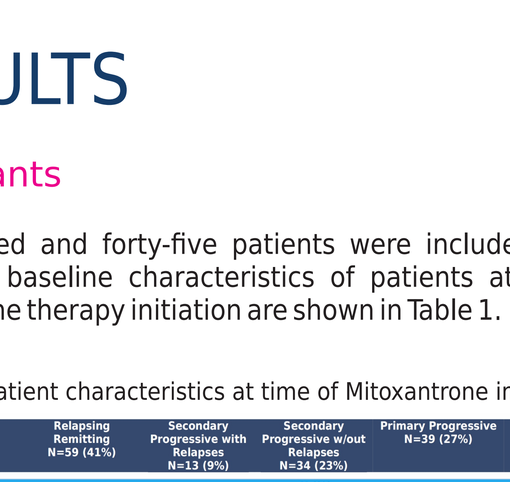

FIGURE 1: Annual relapse rate in relapsing patients

The mean EDSS score at MTX entry was significantly higher in SP without relapses patients (p=0.001) (Fig.2).

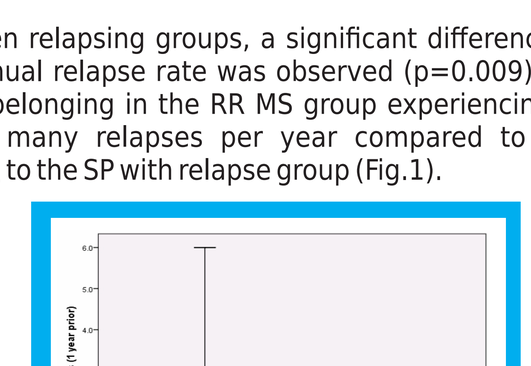

FIGURE 2: EDSS Scores at time of MTX initiation

Patient adherence

Eighty - three patients (57.3%) completed the study reaching a cumulative dose of 140-160 mg of Mitoxantrone intravenously within a period of 2 years.

Sixty-two patients (42,7%) discontinued treatment protocol: 22 patients (37.3%) of the worsening RR group, 5 (38.5 %) of the secondary progressive with relapses group, 17 (50%) of the secondary progressive without relapses group and 18 (46.2 %) of the primary progressive group.

Main causes of discontinuation were patient's decision/ treatment ineffectiveness (28 patients – 19%), and therapy related adverse events (34 patients - 23%). Cardiovascular side effects led to treatment discontinuation in 12 patients (8%), psychological /psychiatric side-effects in 10 patients (7%), gastrointestinal side effects in 4 patients (3%), white blood cell dyscrasias in 3 patients (2%), allergic reaction in 1 patient (0.7%) and hair loss in 1 patient (0.7%).

Safety and tolerability

The most frequently reported adverse drug reactions were: cardiovascular side effects (23 patients – 16 %), psychological /psychiatric side-effects (20 patients, 14%), gastrointestinal side effects (17 patients, 12%), biochemical abnormalities (10 patients, 7%), white blood cell dyscrasias (9 patients, 6 %) and somatic pain (5 patients, 3 %).

Two patients (1,4%) died one year after completing Mitoxantrone treatment: One due to leukemia and the other due to thrombopenia and brain hemorrhage.

Efficacy

Worsening relapsing remitting patients concluding study period (N= 37):

At time of treatment completion, the mean annual relapse rate (ARR) was 1,1 for the RRMS completers, demonstrating a 53% reduction from baseline (p<0.001).

15 patients (41%) were relapse-free. 10 patients (27%) had a relapse reduction of 50% or greater. 12 patients (32%) did not show any significant change from baseline or had an increase in the number of relapses (Fig.3).

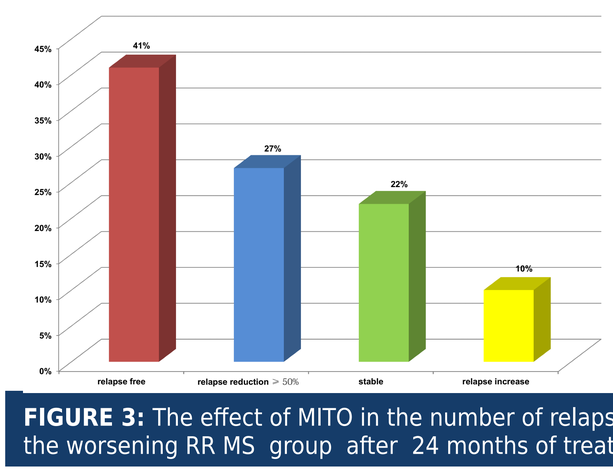

FIGURE 3: The effect of MITO in the number of relapses in the worsening RR MS group after 24 months of treatment

2 patients (5%) showed improvement on the EDSS by 0.5 point. 14 patients (38%) remained stable.11 patients (30%) had a worsening in their EDSS score by 0.5 points, 7 patients (19 %) by 1 point and 3 patients (8 %) by 1.5 points.

The mean worsening of EDSS for the two years of study period was 0.4 whereas the mean worsening of EDSS during the 2 year pre-treatment period was 1.4. A significant reduction of 71% in the rate of disease progression was observed compared to baseline (p<0.001) (Fig.5).

Secondary progressive with relapses patients concluding study period (N= 8):

At time of treatment completion, the mean ARR for the SP with relapses completers was 0.2, signifying an 82% reduction from baseline (p=0.015).

6 patients (75%) were relapse-free. 1 patient (12.5%) had a relapse reduction of 50% and 1 patient (12.5%) did not show any significant change from baseline (Fig.4).

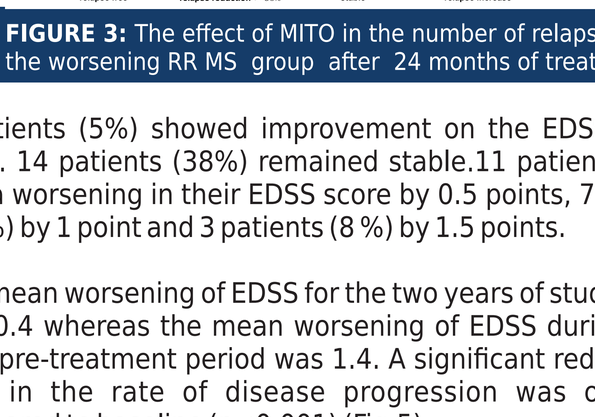

FIGURE 4: The effect of MITO in the number of relapses in the secondary progressive with relapses MS group after 24 months of treatment

2 patients (25%) remained stable. 3 patients (37.5%) had worsening in EDSS by 0.5 points, 2 patients (25%) by 1 point and 1 patient (12.5 %) by 1.5 points.

No significant reduction was observed in the disease progression of patients with relapsing SP MS between the two years of MTX treatment and the two-year pre-treatment period (p=0.111) (Fig.5).

Secondary progressive without relapses patients concluding study period (N= 17):

After completing the two years of our study, the EDSS score of 1 patient (6%) improved by 0,5 points. 4 patients (24%) remained stable. The EDSS score in 8 patients (47%) worsened by 0.5 points, in 2 patients (12%) worsened by 1 point, in 1 patient (6%) worsened by 1.5 points and in 1 patient (6%) worsened by 2,5 points.

The mean worsening of EDSS for the two years of study period was 0.6 whereas the mean worsening of EDSS during the 2 year pre-treatment period was 1. A significant reduction of 40% in the rate of disease progression was observed compared to baseline (p=0.031) (Fig.5).

Primary progressive patients concluding study period (N= 21):

After completing the two years with MTX treatment, the EDSS score of 1 patient (5 %) improved by 1,5 points and of another patient (5%) by 0,5 points. 5 patients (24%) remained stable. The EDSS score in 4 patients (19 %) worsened by 0.5 points, in 1 patient (5%) worsened by 1 point, in 5 patients (24%) by 1,5 points, in 2 patients (9.5%) by 2 points and in 2 patients (9.5%) by 2,5 points.

No significant reduction was observed in the disease progression of patients with PP MS between the two years of MTX treatment and the two-year pre-treatment period (p=0.416) (Fig.5).

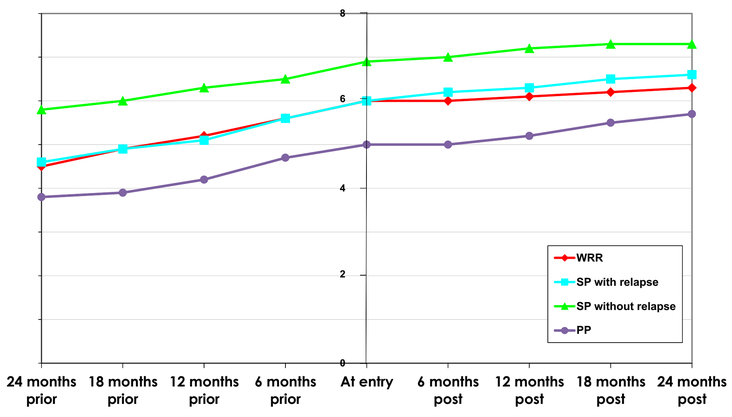

FIGURE 5: Changes in EDSS scores before and after treatment with Mitoxantrone

Overall results (N=84)

Linear regression analysis demonstrated that none of the baseline patient characteristics (sex, age of MS onset, MS duration, baseline annual relapse rate, baseline EDSS, prior use of immunotherapy, or number of MTX treatments) predicted disability progression in our patients.

The number of MTX treatments was however negatively correlated with the annual relapse rate of our relapsing patients (r = - 0.399, p=0.007), indicating that a higher cumulative MTX dose reduced the risk of patients experiencing a relapse.

When all types of MS were taken into account, the mean worsening of the EDSS score in the two years of MTX treatment in patients completing the study was 0.6, whereas the mean worsening of EDSS during the 2 year pre-treatment period was 1.2. Overall, a significant reduction of 50% in the rate of disease progression was observed compared to baseline (p<0.001).

Twenty-one of our relapsing completers (47%) remained relapse-free throughout the whole treatment period.

Finally, thirty of our patients (20%) remained stable or even improved throughout the two years of Mitoxantrone treatment (Fig.6).

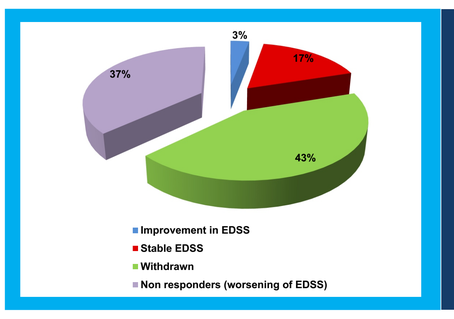

FIGURE 6: Patient response to MTX treatment

CONCLUSIONS

Mitoxantrone was proved to be effective in reducing relapse frequency in patients with worsening Relapsing Remitting and Secondary Progressive Multiple Sclerosis. One third of our relapsing patients completing the study became relapse free during the two years of treatment.

Mitoxantrone was also proved to be beneficial to patients with Relapsing-Remitting and Secondary Progressive without relapses MS in terms of delaying disease progression. It has however failed to demonstrate any statistically significant effect from its off-label use in patients with Primary Progressive MS, even though 18% of our PP patients remained stable or improved during the two years of treatment.

In conclusion, Mitoxantrone seems to be a useful and clinically effective drug in reducing or preventing disability and disease exacerbations in patients with MS to whom prior therapeutic approaches have failed.

Nevertheless, the high percentage of drop-outs attributed to low patient compliance and/or frequency and severity of adverse events has proved to be a major limitation in the wider use of Mitoxantrone in our population.