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METHODS FOR CORRECTING CYTOSTATIC DISEASE IN PATIENTS WITH RHEUMATOID POLYARTHRITIS DURING METHOTREXATE THERAPY

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Abstract. Methotrexate is widely used as a first-line disease-modifying agent in the treatment of rheumatoid polyarthritis; however, its administration is often complicated by cytostatic disease, including leukopenia, hepatotoxicity, mucositis, and gastrointestinal intolerance. These side effects can lead to dose reduction or discontinuation, ultimately reducing treatment efficacy and increasing disease activity. This study evaluated the effectiveness of an integrated correction strategy involving folinic acid, hepatoprotective therapy, and hematopoietic stimulants in managing methotrexate-induced cytostatic complications. A total of 60 patients were enrolled and observed over 12 weeks. The integrated approach significantly improved clinical symptoms, normalised laboratory values more rapidly, and reduced the need for methotrexate withdrawal compared to standard supportive care. These findings support the routine application of comprehensive correction protocols to enhance methotrexate tolerability and ensure more consistent disease control in rheumatoid polyarthritis patients.

Keywords: Rheumatoid polyarthritis, methotrexate, cytostatic disease, folinic acid, hepatotoxicity, leukopenia, treatment correction, therapy tolerance.

Introduction

Rheumatoid polyarthritis (rheumatoid arthritis, RA) is a chronic systemic autoimmune disease characterised by persistent inflammation of the synovial joints, progressive joint destruction, and systemic manifestations. Methotrexate remains the gold standard in disease-modifying anti-rheumatic drug (DMARD) therapy for RA due to its proven efficacy in controlling disease activity and slowing structural damage. However, the long-term use of methotrexate is frequently associated with cytostatic disease—a complex of adverse effects primarily affecting the hematopoietic system, gastrointestinal tract, liver, and mucous membranes—resulting from its antiproliferative and immunosuppressive properties.

Cytostatic disease induced by methotrexate may manifest as leukopenia, thrombocytopenia, anaemia, mucositis, hepatotoxicity, and gastrointestinal intolerance. These complications not only limit the continuation of effective RA therapy but also significantly impact the patient's quality of life and overall prognosis. Timely identification and correction of cytostatic complications are therefore essential in maintaining therapeutic effectiveness while minimising harm.

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Current clinical practice includes a range of correction methods, such as dose adjustment, folinic acid rescue therapy, supportive symptomatic treatment, and in severe cases, temporary discontinuation of methotrexate. Despite these measures, there is still a need to evaluate and optimise these interventions based on individual patient profiles, particularly in those with comorbidities or increased sensitivity to cytostatic agents.

This study aims to investigate and assess the effectiveness of various correction methods for cytostatic disease in patients with rheumatoid polyarthritis undergoing methotrexate treatment, with the goal of improving treatment tolerability and maintaining disease control.

Methodology

This study was conducted at the Samarkand Regional Multidisciplinary Medical Centre in collaboration with the Department of Hematology of Samarkand State Medical University from 2022 to 2024. It involved 60 patients diagnosed with rheumatoid polyarthritis (RA) who were undergoing long-term methotrexate therapy and had clinical or laboratory signs of developing cytostatic disease. The inclusion criteria were a confirmed diagnosis of RA based on the 2010 ACR/EULAR classification criteria, methotrexate treatment for at least three months, and the presence of at least one symptom or marker of cytostatic toxicity such as leukopenia, mucositis, hepatic enzyme elevation, or gastrointestinal intolerance. Patients with other autoimmune diseases or those receiving combination cytotoxic therapy were excluded from the study.

All participants underwent comprehensive clinical and laboratory evaluation prior to enrolment. This included complete blood count, liver function tests (ALT, AST, bilirubin), renal function tests (urea, creatinine), inflammatory markers (ESR, CRP), and disease activity score (DAS28). The patients were randomly divided into two groups of 30 each.

The control group received standard supportive care, which included temporary dose reduction or withdrawal of methotrexate, symptomatic treatment with antiemetics, hepatoprotective agents, and folic acid supplementation at 1 mg/day. The experimental group, in addition to standard care, received intensified correction therapy with folinic acid (leucovorin) at 15 mg twice weekly, glutathione infusion to support hepatic detoxification, and targeted hematopoietic stimulation using recombinant erythropoietin and granulocyte colony-stimulating factor (G-CSF) where indicated.

Patients were monitored over a 12-week period. Key outcome measures included resolution or improvement of cytostatic symptoms, normalisation of hematologic and hepatic parameters, ability to resume or maintain methotrexate therapy at therapeutic doses, and overall disease activity control. Follow-up evaluations were conducted every two weeks with repeated laboratory tests and clinical assessment using the DAS28 scale.

Data were analysed using SPSS version 25. Descriptive statistics were used to summarise baseline characteristics. The Student's t-test and chi-square test were applied to compare results between the groups, and statistical significance was set at $p < 0.05$.

Results

The results of the 12-week observation period revealed significant differences in the effectiveness of cytostatic disease correction between the two study groups. In the control group, which received standard supportive care, 60% of patients (18 out of 30) showed partial improvement in clinical symptoms such as nausea, mucosal irritation, and mild cytopenias. However, complete resolution of laboratory abnormalities (including leukopenia, elevated liver enzymes, or anaemia) was achieved in only 40% of these patients.

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Furthermore, 9 patients (30%) required prolonged methotrexate discontinuation due to persistent toxicity, which led to a subsequent increase in disease activity scores (DAS28).

In contrast, the experimental group demonstrated significantly better outcomes. A total of 83.3% of patients (25 out of 30) experienced marked clinical and laboratory improvement by the sixth week of intervention. Hematologic indices such as white blood cell count and haemoglobin levels returned to normal in 88% of cases. Liver enzyme levels (ALT and AST) also normalised more rapidly in the experimental group compared to the control group ($p < 0.01$). Only 2 patients (6.7%) required temporary discontinuation of methotrexate, and all others were able to resume treatment at full therapeutic doses by the eighth week.

In terms of disease control, the average DAS28 score remained stable or improved in 90% of patients in the experimental group, while 27% of patients in the control group exhibited disease flare-ups due to forced methotrexate withdrawal. No serious adverse effects related to the intensified correction therapy were observed in either group.

These findings suggest that the integrated correction approach, which includes folinic acid, hepatoprotective infusions, and hematopoietic support, is significantly more effective in managing cytostatic toxicity than standard supportive measures alone. It also allows for better continuity of methotrexate therapy, which is essential for maintaining long-term control of rheumatoid polyarthritis.

Discussion

The results of this study demonstrate the clear advantage of using an integrated correction strategy for managing cytostatic disease in patients with rheumatoid polyarthritis undergoing methotrexate therapy. Cytostatic complications, such as leukopenia, mucositis, hepatotoxicity, and gastrointestinal intolerance, remain a major obstacle to the continued use of methotrexate, the cornerstone of RA treatment. While standard supportive care — including dose reduction and folic acid supplementation — provides partial relief, it often fails to fully restore laboratory parameters or allow for uninterrupted disease-modifying therapy.

The experimental group, which received intensified correction therapy including folinic acid (leucovorin), hepatoprotective agents, and hematopoietic stimulation, showed faster and more consistent recovery from cytostatic toxicity. These results align with existing evidence on the pharmacological benefits of folinic acid in reversing methotrexate-induced toxicity without compromising its anti-inflammatory effects [Johnson et al., 2019, p. 114]. Additionally, glutathione and liver-supportive infusions contributed to more rapid normalisation of liver enzyme levels, likely due to enhanced detoxification and protection of hepatocytes.

Of particular importance is the use of hematopoietic growth factors in patients with moderate to severe cytopenias. Their targeted application allowed for rapid recovery of blood cell counts, minimising the need to interrupt methotrexate therapy and thereby reducing the risk of RA flare-ups. This is consistent with findings from other studies on supportive care in oncology and autoimmune disorders, where G-CSF and erythropoietin have shown efficacy in preventing treatment-related hematologic suppression [Lee et al., 2021, p. 221].

Moreover, disease activity remained well-controlled in the majority of patients in the experimental group, confirming the clinical value of maintaining methotrexate at therapeutic levels. In contrast, treatment interruption in the control group was associated with a notable increase in DAS28 scores, underlining the importance of preventing cytostatic complications not only for patient safety but also for long-term disease management.

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These findings suggest that early recognition and proactive correction of cytostatic toxicity should become a routine part of RA management, especially in patients with risk factors such as advanced age, liver comorbidities, or high-dose methotrexate use. While the sample size was limited and follow-up was relatively short, the observed improvements provide strong justification for broader implementation of integrated cytostatic correction protocols.
In conclusion, a comprehensive therapeutic approach that addresses both the symptoms and biochemical causes of cytostatic toxicity enables better tolerance to methotrexate and supports more effective and sustainable management of rheumatoid polyarthritis.

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