Adverse Effects of Thalidomide Administration, in Patients with Myeloma Multiplex?

Svetlana Balkanov Krstevska¹, Tatjana Sotirova¹, Sonja Stavrik Genadieva¹, Lidija Cevreska¹, Aleksandar Stojanovik¹, Trajan Balkanov²

University of Hematology Clinic, Medical faculty, Skopje, Republic of Macedonia¹
Department of Pharmacology, Medical Faculty University “St Ciril and Methodius”, Skopje, Republic of Macedonia²

Corresponding author: Svetlana B. Krstevska, MD. University of Hematology clinic, Medical faculty, University of Skopje, Republic of Macedonia.

ABSTRACT

Introduction: Myeloma multiplex is defined by the presence of monoclonal plasma cell population in the bone marrow >10%, M protein in the serum and/or urine, and clinical evidence of end organ damage like hypercalcemia, renal failure, anemia, or bone lesions. In the most hematologic malignancies the role of induction treatment is to achieve complete remission (CR). Thalidomide became a new therapeutic approach but use of Thalidomide as a single agent or combination with steroids or chemotherapy is associated with several side effects like deep vein thrombosis (DVT), peripheral neuropathy (PN), constipation, somnolence, pyrexia, pain, fatigue osteonecrosis of jaw, and teratogenicity that is the most worrying adverse event. Risk of appearance of DVT increased if we use combination of Thalidomide plus Dexamethasone plus cytotoxic chemotherapy such Cyclophosphamide. >30% DVT usually occurs during the first months of treatment and is more frequent in newly diagnosed patients with a high tumor burden. The second side effect is peripheral neuropathy (PN) which occurs in 50% of patients with MM treated with Thalidomide plus Dexamethasone and chemotherapy. Patients and methods: Eighty patients of both sexes (43 males and 37 females) at the age of 31-81 (median range 58 years) with MM, were treated–one group with combinations of Thalidomide plus Dexamethasone plus Cyclophosphamide (CyThalDex) 4 cycle (>4months), and the other group with Thalidomide plus Dexamethasone plus Melphalan (MPT), (>4month) and third group with high dose of chemotherapy and continue with ThalDex (TD), the fourth group with CyThalDex, > than 5 cycles, and the fifth group with ThalDex (TD) only. Results: It is obvious while myelo-suppression is very rare, the incidence of nonhematologic side effects is high and dose dependent. Eight (or 10%) patients that developed DVT and CVI were initially treated with antiaggregation therapy of Aspirin 100mg per day, but those that already developed were treated with low dose of Heparin 40000 iE per day in ten days and continued with oral anticoagulants therapy. However, besides the given therapy in four (or 5%) patients there was exitus letalis. PN was developed in twentyone patients (or 26.25%) from the total number of patients treated with Thalidomide, in ten patients the dosage of Thalidomide was decreased to 50mg per day, in one patient with Epi attacks it was interrupted and the other was with paresis n.occulomotorius and n.abducens. Conclusions: Patients treated with thalidomide have an increased risk of arterial thromboembolism, including myocardial infarction and cerebrovascular events, in addition to the established risk of venous thromboembolism, but most patients who presenting DVT or some of thromboembolic events have had identifiable risk factors. The prolonged exposure to Thalidomide seems to induce resistance of MM reducing overall survival (OS). We must evaluate consolidation and maintenance therapies with Thalidomide, determinate which regimens provide a highness benefit with favorable side effect profiles in specific subgroups of patients.

Key words: Myeloma multiplex (MM), Deep Vein Thrombosis (DVT), Peripheral Neuropathy (PN), Thalidomide.

1. INTRODUCTION

Myeloma multiplex is defined by the presence of monoclonal plasma cell population in the bone marrow >10% M protein in the serum and/or urine, and clinical evidence of end organ damage like hypercalcemia, renal failure, anemia, or bone lesions (1, 2). In the most hematologic malignancies the role of induction treatment is to achieve complete remission (CR). In MM this has been possible only with the introduction of high-dose therapy plus autologous stem cell transplantation (ASCT) in patients eligible for transplantation. At the end the clinical results from many studies were poorest, CR was possible only in 20-40% and 40%-55% CR/VGPR (very good partial remission). Of course treatment of MM patients ineligible for transplantation, conventional therapy was consist of alkylating–based regimens mainly melphalan plus prednisolone (MP) or dexamethasone, with these regimens CR rate was <5% with median survival of approximately 3 years (3, 4). The introduction of novel agents in the induction treatment is changing...
this story. Thalidomide became a new therapeutic approach and its derivatives such lenalidomide, with their antiangiogenic properties via inhibition of vascular endothelial growth factor (VEGF) and β−−−−fibroblast growth factor (FGF), directly inhibits growth and survival of myeloma cells. Of course we didn’t ignore immunomodulatory properties like blocks the activation of nuclear factor−−κβ and inhibits the production of proinflammatory citokines and increase antymyeloma immunity by stimulating T lymphocytes and natural killer cells (2, 5, 6).

Clinical efficacy of thalidomide is evident: in relapsed/refractory MM approximately 45% induces objective response, in newly diagnosed patients with MM is obvious CR or VGPR (4). But use of thalidomide as a single agent or combination with steroids or chemotherapy is associated with several side effects like deep vein thrombosis (DVT), peripheral neuropathy (PN) characterized by numbness, paresthesia or pain in the hands or in the feet or legs, death from DVT, or embolio pulmonum (EP), the most serious and others like constipation, somnolence, pyrexia, pain, fatigue osteonecrosis of jaw (7, 8, 9). Teratogenicity is the most worrying adverse event and although MM usually affects postmenopausal women, special programs have been designed to avoid drug exposure in women of child-bearing potential. The incidence of DVT with Thalidomide alone is 3−4% in new MM, and 2−4% more in refractory disease (10). The incidence of DVT and PN were 12% and 30% in the MPT. But the addition of dexamethasone, especially at high dose markedly increases the risk, specially in those patients with new disease. In newly diagnosed MM, incidence of DVT, treated with Thal/Dex is 14−26% and 2−8% more in those with relapsed or refractory disease without thromboprophylaxis (3, 4). Risk of appearance of DVT increased if we use combination of Thalidomide plus Dexamethasone plus cytotoxic chemotherapy such Cyclophosphamide. >30% DVT usually occurs during the first months of treatment and is more frequent in newly diagnosed patients with a high tumor burden (11, 12). The second side effect is peripheral neuropathy (PN) which occurs in 50% of patients with MM treated with Thalidomide and Dexamethasone and chemotherapy (4, 7, 8). Constipation occurs 100%, sedation 87% and skin lesion but for these side effects patients developed tolerance. Very important is the role of Thalidomide in relapsed or refractory MM patients who has show courage results (7).

2. MATERIAL AND METHODS

Eighty patients of both sexes (43 males and 37 females) at the age of 31−81 (median range 58 years) with MM were treated one group with Thalidomide plus Dexamethasone plus Cyclophosphamide (CyThalDex) 4 cycle (>4months), and the other group with Thalidomide plus Dexamethasone plus Melphalan (MPT), (>4months) and third group with high dose of chemotherapy and continue with ThalDex (TD), the fourth group with CyThalDex, > than 5 cycles, and the fifth group with ThalDex (TD) only. Patients have been evaluated for every check−up in our Daily hospital. Patients were started with Thalidomide 100mg/per day with or without Dex and chemotherapy. During the course of therapy, patients were monitored every 15 days and all possible adverse effects were evidenced in checklist.

Those patients that developed life threatening complication like DVT or EP or Thrombosis of sinus sagittalis were interrupted with treatment with Thalidomide but from the total number of patients this complication was shown in small number of patients. With those patients that developed PN as a complication from Thalidomide, the application of the dosage was decreased to 50mg per day in one temporary period, when the MM patient’s parameters allowed that. Our study of patients presents eight patients (or 10%) developed DVT. Twentyone patients (or 26.25%) developed PN (one patient of the researched group developed paresis of n.occulomotorius et n.abducens and one patient developed Epi attacks). Five (5) patients (or 6.25%) developed both DVT and PN. Four patients (or 5%) ended with exitus letalis from which two (or 2.5%) of them with unexpected death from Embolio pulmonum (EP), one patient (or 1.25%) from Thrombosis of sinus sagitallis and one patient (or 1.25%) from unknown cause. One patient was treated successfully after the complication of EP. Other complications that were developed in our group of patients after the application of Thalidomide were swollen knives in four patients (or 5%), obstipation in seventytwo patients (or 90%), vomitus and sickness and primary intolerability of medication shown in four patients (or 5%), one patient showed reactivation of B Hepatitis and one patient showed secondary carcinoma in vesica urinaria (Table 1).

The time of application of Thalidomide didn’t correlate with the aspect of DVT. Those patients who were eligible for autologous transplantation, with or without side effects of Thalidomide administration, were transplanted, but those patients who were ineligible for auto transplantation (coexisting of co-morbidity and elderly patients) were treated only with TD. The age of patients and organ damage predicted the clinical response in MM patients, but they didn’t predict the side effects of novel agents. So the question was: What is the optimal duration of induction treatment with novel agents?

3. RESULTS

It is obvious while myelo-suppression is very rare, the incidence of nonhematologic side effects is high and dose dependent. Eight (or 10%) patients that developed DVT and CVI were initially treated with antiaggregation therapy of Aspirin 100mg per day, but those that already developed were treated with low dose of Heparin 40000 iE per day in ten days and continued with oral anticoagulans therapy. However, besides the given therapy in four (or 5%) patients there was exitus letalis. PN

| Therapy | No of patients | Percent | DVT | PN | EP | CVI | DVT plus PN |
|---------|----------------|---------|-----|----|----|-----|-------------|
| 4 cycle CyThalDex | 18 | 22.5 | 5 | 2 | 3 | 1 |
| MPT | 18 | 22.5 | 4 |
| High dose of chemo plus TD | 10 | 12.5 | 1 | 1 |
| > than 5 cycles CyThalDex | 20 | 25 | 1 | 11 | 1 | 4 |
| TD | 14 | 17.5 | 1 | 3 |
| Total | 80 | 100 | 8 | 21 | 3 | 1 | 5 |

Table 1. Correlation of use of Thalidomide with the aspect of DVT
was developed in twentyone patients (or 26.25%) from the total number of patients treated with Thalidomide, in ten patients the dosage of Thalidomide was decreased to 50mg per day, in one patient with Epi attacks it was interrupted and the other was with paresis n. occulomotorius and n. abducens.

4. DISCUSSION AND CONCLUSION

Patients treated with thalidomide have an increased risk of arterial thromboembolism, including myocardial infarction and cerebrovascular events, in addition to the established risk of venous thromboembolism, but most patients who presenting DVT or some of thromboembolic events have had identifiable risk factors. Action should be taken to minimize all modifiable risk factors for thromboembolizing events (e.g. smoking, hypertension and hyperlipidemia) and of course application of thromboprophylaxis in patients suitable for treatment with thalidomide (13, 14, 15).

Thalidomide seems to be good choice for patients with MM who are eligible for autologous transplantation, considering their toxicity profile (1). Firstly, PN and Thalidomide, the lack of correlation between cumulative dose and outcome, a limited administration is suggested. The choice of first relapse treatment will probably depend on the previous treatments and on the true evaluation of the risk/benefit ratio in function of the toxicity profile of Thalidomide. Thalidomide has an excellent role in consolidation phase of this chronic disease like MM, rather than maintenance, but with lower dose of Thalidomide and for a limited period. Moreover, a prolonged exposure to Thalidomide seems to induce resistance of MM reducing overall survival (OS). We must evaluate consolidation and maintenance therapies with Thalidomide, determinate which regimens provide a highness benefit with favorable side effect profiles in specific subgroups of patients.

Conflict of interest: none declared.

REFERENCES

1. Sirohi B, Powles R. Multiple myeloma. Lancet. 2004; 363; 875-887.
2. Durie BG, Harousseau J, Miguel J. et al. International uniform response criteria for multiple myeloma. Leukemia. 2006; 20: 1467-1473.
3. Rajkumar SV, Hayman S, Gertz MA. et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol. 2002; 20: 4319-4323.
4. Weber D, Rankin K, Gavino M. et al. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol. 2003; 21: 16-19.
5. Singhal S, Mehta J, Deskin J. et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med. 1999; 341: 1565-1571.
6. Kumar S, Gertz MA, Dispensieri A. et al. Response rate, durability of response, and survival after thalidomide therapy for relapsed multiple myeloma. Mayo Clin Proc. 2003; 78: 34-39.
7. Richardson P, Schlossman R, Jagannath S. et al. Thalidomide for patients with relapsed multiple myeloma after high-dose chemotherapy and stem cell transplantation: Results of an open-label multicenter phase 2 study of efficacy, toxicity and biological activity. Mayo Clin Proc; 2004; 79: 875-882.
8. Osman K, Comenzo RL, Rajkumar SV. Deep venous thrombosis and thalidomide therapy for multiple myeloma. N Engl J Med. 2001; 344: 1951-1952.
9. Zangari M, Barlogie B, Thertulien R. et al. Thalidomide and deep vein thrombosis in myeloma multiplex: risk factors and effect in survival. Clin Lymphoma. 2003; 4: 32-35.
10. Bennet CL., Schumoki GT, Kwaan HC, Raisch DW. High incidence of thalidomide associated deep vein thrombosis and pulmonary emboli when chemotherapy is also administered. Blood. 2001; 98: A863.
11. Palumbo A, Bringen S, Caravita T. et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomized controlled trial. Lancet. 2006; 367: 825-831.
12. Zangari L, Barlogie B, Anaissie E. et al. Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemotherapy: effects of prophylactic therapy anticoagulation. Br J Haematology. 2004; 126: 725-721.
13. Baz R, Li L, Kottke-Marchant K. et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline based chemotherapy for multiple myeloma. Mayo Clinic Proc. 2005; 80: 1568-1574.
14. Minnema MC, Breitkreutz I, Anwerda JJ. et al. Prevention of venous thromboembolism with low molecular-weight heparin in patients with multiple myeloma treated with thalidomide and chemotherapy. Leukemia. 2004; 18: 2044-2046.
15. Dimopoulos MA, Anagnostopoulus A, Weber D. Treatment of plasma cell dyscrasia with thalidomide and its derivatives. J Clin Oncol. 2003;21: 4444-4452.