Published in final edited form as:
Br J Haematol. 2010 June ; 149(5): 706–710. doi:10.1111/j.1365-2141.2010.08145.x.

Anti-thymocyte Globulin plus Etanercept as Therapy for Myelodysplastic Syndromes (MDS): a Phase II Study

Bart L. Scott[1,2], **Aravind Ramakrishnan**[1,2], **Mark Fosdal**[1], **Barry Storer**[1,2], **Pamela Becker**[2], **Steve Petersdorf**[1,2], and **H. Joachim Deeg**[1,2]

[1]Fred Hutchinson Cancer Research Center, Seattle, Washington

[2]University of Washington School of Medicine, Seattle, Washington

Summary

Immunosuppressive therapies have proven valuable in treating patients with myelodysplastic syndromes (MDS). We evaluated the combination of equine anti-thymocyte globulin (ATGAM®) and the soluble TNF receptor etanercept (Enbrel®) in a phase II trial. Twenty-five patients with MDS (4-RA, 2-RARS, 15-RCMD, 3-RCMD-RS, 1-RAEB-1) in IPSS risk groups low (n=11) or intermediate-1 (n=14) were enrolled. All patients were platelet or red cell transfusion dependent. Nineteen patients completed therapy with ATG at 40 mg/kg/day for four consecutive days, followed by etanercept, 25 mg subcutaneous twice a week for 2 weeks, every month for 4 months. Thirteen patients had hematological improvement (HI)-erythroid, 2 HI-neutrophil, and 6 HI-platelet. One patient with a co-existing diagnosis of multiple sclerosis and rheumatoid arthritis had a complete remission. The overall response by intent to treat analysis among the 25 patients was 56% (95% CI 35–56%). Four patients did not complete their first course of therapy and one patient did not survive to the 8-week post-treatment assessment. Among patients who completed treatment and survived to the 8-week assessment, 70% had at least hematological responses lasting for at least 5 to more than 36 months. Thus, combination therapy with ATG and etanercept was active and safe in patients with MDS.

Keywords

MDS; etanercept; ATG; immunosuppressives; hematopoiesis

Introduction

Patients with MDS who respond to immunosuppressive therapy tend to have a better prognosis with low risk of progression to AML and prolonged survival in comparison to non-responders (Molldrem *et al*, 2002). This is likely because responders to immunosuppressive therapy have a disease with a different pathogenic mechanism leading to the development of MDS. Many patients with MDS overexpress the pro-inflammatory/pro-apoptotic cytokine TNF-α in the bone marrow (Kitagawa *et al*, 1997; Deeg *et al*, 2000). Etanercept is a recombinant soluble TNF receptor (TNF alpha p75 fusion protein) that neutralizes TNF-α, and we have shown that in vitro hematopoietic colony formation from the marrows of patients with MDS is enhanced in the presence of etanercept (Gersuk *et al*, 1998). Initial studies with etanercept showed evidence of hematologic responses in all three

Corresponding author: Bart L. Scott, MD, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue N, D1-100, Seattle, WA 98109-1024, bscott@fhcrc.org.

Conflicts of Interest Disclosure
There are no relevant conflicts to disclose.

cell lines; however, with etanercept as a single agent, responses were in the range of 0%–33% (Rosenfeld & Bedell, 2002; Maciejewski *et al*, 2002; Deeg *et al*, 2002).

Others have shown that therapy of MDS with anti-thymocyte globulin (ATG) resulted in a reduction or loss of clonally expanded T-lymphocytes and hematopoietic recovery (Molldrem *et al*, 1998; Kochenderfer *et al*, 2002). These results were supported by in vitro work, which showed improved hematopoiesis upon T cell removal (Molldrem *et al*, 1998) and implied a T-cell mediated inhibition of hematopoiesis as a possible pathogenic mechanism in some patients with MDS. Activated T cells are also a rich source of TNF-α.

In a phase II trial, ATG was effective treatment for transfusion dependent MDS patients, with 44% having some response and 12% becoming transfusion independent (Molldrem *et al*, 1997). However, not all subsequent trials have shown the same response rates (Steensma *et al*, 2003; Killick *et al*, 2003). Various factors have been examined in regards to their predictive power for response to immunosuppressive therapy. Some authors have concluded that low IPSS scores and bone marrow hypocellularity are associated with hematological responses to ATG (Lim *et al*, 2007). Other studies have shown an association of response to ATG with HLA-DR 15, younger age, and shorter duration of transfusion dependence, but not with bone marrow hypocellularity (Saunthararajah *et al*, 2003; Saunthararajah *et al*, 2002). There appears to be no difference in efficacy between horse and rabbit ATG (Stadler *et al*, 2004), although these preparations have not been compared in a phase III randomized study.

We conducted a pilot study with a combination of ATG and etanercept in 14 patients with low-risk MDS and achieved an overall response rate of 46% (Deeg *et al*, 2004). There was a correlation between pre-treatment low aberrancy of marrow cells by flow cytometry and probability of response, and between “normalization” of flow cytometric aberrancies in the marrow after 8 weeks of treatment, and prolonged hematologic responses; conversely, worsening flow scores correlated with disease progression (Scott *et al*, 2008). The purpose of the present study was to further asses the response rates and toxicities of ATG and etanercept therapy in patients with low or int-1 risk MDS.

Methods

Twenty five patients 53–85 (median 64) years of age with low or intermediate-1 (int-1) risk MDS were enrolled (Table I). All presented with single or multilineage cytopenias (ANC <1500/μL, Hgb <10g/dL, or platelets <100,000/μL) or transfusion requirements of at least two units of packed red blood cells over an 8-week period. All patients enrolled were platelet or red blood cell (RBC) transfusion dependent or both. All patients had given written informed consent according to the IRB-approved protocols at the Fred Hutchinson Cancer Research Center. Patients who previously received ATG or hematopoietic stem cell transplants were excluded. Patients could not have received cytotoxic therapy, hematopoietic growth factors, immunomodulatory or other experimental therapy for their low to intermediate-1 MDS in the previous two weeks.

A pretreatment history was taken regarding transfusions, hematologic parameters at diagnosis, and interval from diagnosis to enrollment on protocol. Blood chemistries, complete blood cell counts with differentials and bone marrow aspirates and biopsies, including flow cytometry, karyotype analysis, and morphologic analysis were performed, and the diagnosis of MDS was made using World Health Organization (WHO) criteria (Vardiman *et al*, 2002). Patients were followed for transfusion requirements for 16 weeks following completion of ATG therapy (while still receiving etanercept). Bone marrow examinations were performed at 8 and 16 weeks after ATG therapy.

Horse ATG (ATGAM) was administered intravenously at 40 mg/kg/day for four consecutive days, given as an 8–12 hour infusion daily. All patients were premedicated with methylprednisolone 1 mg/kg IV prior to each infusion of ATG. After completion of 4 days of ATG, the patients received etanercept, 25 mg s.c. twice weekly, for cycles of two weeks on and two weeks off for a total of 16 weeks in patients who showed responses at eight weeks. Etanercept was self-administered at home or given in a local infusion clinic. Logs were collected from patients to ensure compliance with etanercept administration.

Responses were assessed using the modified guidelines proposed by the International Working Group (Cheson *et al*, 2006) and by flow cytometric scoring (Scott *et al*, 2008). At 8 and 16 weeks after initiation of ATG and etanercept, patients had repeat bone marrow aspirations performed as well as a complete history and exam documenting transfusion requirements. Weekly complete blood cell counts were obtained for the first month and then every other week for the next three months; monthly renal, hepatic, and pregnancy tests for women in childbearing years were also obtained.

Results

There were 25 patients with low or int-1 risk MDS enrolled into this study, and 21 completed treatment with ATG. Of the 4 patients who did not complete ATG therapy, the reasons for withdrawal included: anaphylactic reaction, thrombosis of pre-existing femoral graft, myocardial infarction, and patient preference, respectively. Of the 21 patients who completed the course of ATG, one died of intracranial hemorrhage prior to the first response assessment at 8 weeks. All other patients completed at least 8 weeks of post-treatment follow up, and responses based upon IWG criteria could be assessed. Most patients had anemia as the indication for enrollment into the trial. Of the 25 patients enrolled, only 4 had a hemoglobin ≥ 11 g/dL; 7 had a platelet count ≥ 100,000/μL; and 14 had neutrophil counts ≥ 1,000/μL. A total of 14 patients had some evidence of hematologic improvement for an overall response rate of 56% based upon intent-to-treat analysis (Table II). Among patients who completed the 4-day course of ATG treatment and were evaluable at the 8-week follow up, the overall response rate was 70%. All patients who responded to ATG/etanercept did so by 8 weeks. With a median follow-up of 2 years post-therapy, hematologic improvements were sustained in all patients who responded; the one patient who obtained a complete remission remained in complete remission.

Most major adverse events consisted of symptoms related to the infusion of ATG, including hives, fever, and hypotension. Most of these resolved with slowing the rate of ATG infusion. Seven patients developed a serum sickness-like reaction following discharge from the hospital. The symptoms rapidly resolved with continued administration of steroid therapy for one week post-ATG therapy

Only one patient in this study had more than 5% bone marrow myeloblasts, and this patient had no response to immunosuppressive therapy. The one patient who achieved a complete remission experienced normalization of peripheral blood cell counts and bone marrow findings. This patient was RBC and platelet transfusion dependent before therapy. Interestingly, this patient also had a diagnosis of rheumatoid arthritis and multiple sclerosis, which also improved with immunosuppressive therapy. Prior treatments for rheumatoid arthritis included methotrexate, plaquenil, and steroids. The patient received no prior therapy for multiple sclerosis.

Among the 10 patients with cytogenetic abnormalities, there was only one subject with trisomy 8, and this patient had erythroid and platelet lineage responses with normalization of peripheral blood cell counts following ATG therapy. One patient had complex cytogenetic

abnormalities and did not respond. Other cytogenetic abnormalities included a loss of the Y chromosome in three patients (one response), a deletion 13q in one patient (no response), a deletion 5q in one patient (response), a deletion 20q in two patients (one response), a trisomy 21 in one patient (no response), and a translocation between chromosomes 2 and 11 in one patient (response).

HLA typing (for the determination of HLA-DR15) was available in 18 patients. Ten of these had an HLA-DR15 allele present; none of the subjects was homozygous for HLA-DR15. Six of the 10 patients with HLA-DR15 responded to therapy, compared to 6 of 8 patients without HLA-DR15. Therefore, there was no association between HLA-DR15 and response to ATG plus etanercept therapy in this small subset of patients in whom HLA typing was available.

As we had previously observed a correlation between flow scores and response to therapy (Deeg *et al*, 2004), we were interested in reexamining such a relationship in the present study. Due to changes in the institutional arrangement for flow analysis, we were able to calculate flow scores (Scott *et al*, 2008) only in 10 patients pre-treatment, of whom four had flow scores repeated post-treatment. There were five patients with normal/mildly abnormal scores before therapy, and two of these responded; four patients with intermediate scores, all of whom responded; and one patient with a high flow score who had no response to ATG/etanercept therapy. Among the four patients with post-treatment re-assessment, the flow scores remained unchanged even though they showed evidence of hematologic improvement, based upon IWG criteria.

Discussion

There is agreement that immunosuppressive therapy is effective in some patients with MDS; however, the most appropriate selection of patients to receive immunosuppressive therapy remains controversial. Studies from the NHLBI indicate that younger age, shorter duration of RBC transfusion dependence, and presence of HLA-DR15 are all associated with response to ATG therapy (Saunthararajah *et al*, 2003). There was no correlation between marrow hypocellularity and response to immunosuppression (ATG or cyclosporine). This contrasts with findings by investigators in the UK who found an association between response to ATG and low IPSS score as well as bone marrow hypocellularity (Lim *et al*, 2007). The UK investigators defined hypocellularity as <20% cellularity, whereas the NHLBI investigators identified hypocellularity as <30%, which may account for some differences in the findings between these two studies.

Other investigators have encountered significant toxicity with ATG administration and limited efficacy in an unselected population of patients with MDS (Steensma *et al*, 2003). The phase 2 study by Steensma et al. enrolled only eight patients before reaching a preset stopping rule for toxicity. Importantly, 6 of 8 patients enrolled in that study had more than 5% bone marrow myeloblasts. An update of the NHLBI experience with immunosuppressive therapy (ATG ± cyclosporine) in 126 patients with MDS confirmed that younger age and the presence of HLA-DR15 was associated with an increased probability of response (Sloand *et al*, 2008). Only four subjects in that study were unable to complete ATG therapy. Based on the prior work of these investigators, we restricted accrual into our study to patients with low or int-1 risk MDS and symptomatic cytopenias. On that basis, only one subject with a bone marrow myeloblast count greater than 5% was enrolled; that patient had no evidence of response. We were able to successfully administer ATG therapy to all but four patients with manageable toxicities.

Another controversial area involves the question of whether additional benefits are gained by combining immunosuppressive agents. In the UK study, 42% of patients treated with ATG achieved hematologic responses (Lim *et al*, 2007). In a study conducted at M.D. Anderson Cancer Center, 31 patients with MDS received ATG therapy with an overall response rate of 26% (Yazji *et al*, 2003). In the most recent report from the NHLBI, the overall response rate to ATG was 30% (Sloand *et al*, 2008). The majority of patients in all of these studies had RA/RARS or low/int-1 risk MDS, although the studies did not restrict enrollment on this basis. In the current trial we observed an overall response rate of 56%; however, as mentioned earlier our study was restricted to low/int-1 risk MDS patients. In the NHLBI study, the combination of ATG with cyclosporine was associated with improved response rates (48%) (Sloand *et al*, 2008). Similarly, the present study using a combination of ATG and etanercept showed response rates that were higher than those reported with ATG alone. Several studies have indicated lower response rates following solitary therapy with etanercept (Rosenfeld & Bedell, 2002; Maciejewski *et al*, 2002; Deeg *et al*, 2002) or cyclosporine. This suggests that in order for patients with MDS to achieve a response it is important to reset the ongoing immune dysregulation with ATG therapy. Patients who respond to ATG therapy have a loss in specific T-cell clones, in support of the conept that these patients have an autoimmune mediated disease. (Kochenderfer *et al*, 2002; Molldrem *et al*, 1998) The potential benefits of ATG/etanercept over ATG/cyclosporine are lower toxicity and perhaps improved response rates. Unlike cyclosporine, etanercept may have additional effects outside of T-cell suppression leading to enhanced responses. For example, experiments have documented higher levels of TNF-α in bone marrow samples taken from patients with MDS (Kitagawa *et al*, 1997; Gersuk *et al*, 1998), and TNF-α induced apoptosis may lead to ineffective hematopoiesis particularly in early stages of MDS. (Sawanobori *et al*, 2003) Therefore, the ATG/etanercept combination may have a net advantage in comparison to the ATG/cyclosporine combination.

With the availability of the FDA-approved agents lenalidomide, azacitidine, and decitabine, physicians now have a choice of therapy for patients with MDS. However, there is clearly a subset of patients with MDS who benefit from immunosuppressive therapy. Unlike the FDA-approved agents, ATG can induce prolonged responses following a 4-day course of therapy, whereas the above drugs must be administered on an ongoing basis. Further, patients who respond to ATG therapy typically show prolonged survival with low risk of progression to AML compared to non-responders (Molldrem *et al*, 2002). In our experience, ATG was well tolerated overall with minimal side effects. Important determinants of toxicity included the infusion rate, and the dose and schedule of concurrent steroid therapy. It is possible that the co-administration of etanercept in our study not only improved response rates, but also decreased toxicities associated with ATG infusion.

We were able to enroll 25 MDS patients with low or int-1 risk MDS into this phase 2 study, and all but four subjects were able to complete ATG therapy. In the majority of subjects, side effects were manageable with steroid therapy (given for a short course) and the co-administration of etanercept. Based on an intent-to-treat analysis, the overall response rate was 56%. Responses were seen by 8 weeks in responders. The available evidence indicates that patients with advanced/high grade MDS as indicated by complex cytogenetic changes, increased marrow myeloblasts, or high flow scores are unlikely to respond to immunosuppressive therapy. For patients with low grade MDS, a combination of ATG and etanercept results in higher response rates than observed with ATG alone.

Acknowledgments

Supported in part by grants CA 119599, HL082941, and HL084054.

We thank the hematologic malignancy teams at the Seattle Cancer Care Alliance for their contributions, all patients for their participation in this trial, the research nurse Joanne Greene, our data coordinator Franchesca Nguyen, and Bonnie Larson and Helen Crawford for help with manuscript preparation.

Reference List

1. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans P, Nimer SD, Pinto A, Beran M, de Witte TM, Stone RM, Mittelman M, Sanz GF, Gore SD, Schiffer CA, Kantarjian H. Clinical applications and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006; 108:419–425. [PubMed: 16609072]
2. Deeg HJ, Beckham C, Loken MR, Bryant E, Lesnikova M, Shulman HM, Gooley T. Negative regulators of hemopoiesis and stroma function in patients with myelodysplastic syndrome. Leukemia and Lymphoma. 2000; 37:405–414. [PubMed: 10752992]
3. Deeg HJ, Gotlib J, Beckham C, Dugan K, Holmberg L, Schubert M, Appelbaum F, Greenberg P. Soluble TNF receptor fusion protein (etanercept) for the treatment of myelodysplastic syndrome: A pilot study. Leukemia. 2002; 16:162–164. [PubMed: 11840280]
4. Deeg HJ, Jiang PYZ, Holmberg LA, Scott B, Petersdorf EW, Appelbaum FR. Hematologic responses of patients with MDS to antithymocyte globulin plus etanercept correlate with improved flow scores of marrow cells. Leukemia Research. 2004; 28:1177–1180. [PubMed: 15380342]
5. Gersuk GM, Beckham C, Loken MR, Kiener P, Anderson JE, Farrand A, Troutt AB, Ledbetter JA, Deeg HJ. A role for tumor necrosis factor-α, Fas and Fas-Ligand in marrow failure associated with myelodysplastic syndrome. British Journal of Haematology. 1998; 103:176–188. [PubMed: 9792306]
6. Killick SB, Mufti G, Cavenagh JD, Mijovic A, Peacock JL, Gordon-Smith EC, Bowen DT, Marsh JC. A pilot study of antithymocyte globulin (ATG) in the treatment of patients with 'low-risk' myelodysplasia. British Journal of Haematology. 2003; 120:679–684. [PubMed: 12588356]
7. Kitagawa M, Saito I, Kuwata T, Yoshida S, Yamaguchi S, Takahashi M, Tanizawa T, Kamiyama R, Hirokawa K. Overexpression of tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma by bone marrow cells from patients with myelodysplastic syndromes. Leukemia. 1997; 11:2049–2054. [PubMed: 9447819]
8. Kochenderfer JN, Kobayashi S, Wieder ED, Su C, Molldrem JJ. Loss of T-lymphocyte clonal dominance in patients with myelodysplastic syndrome responsive to immunosuppression. Blood. 2002; 100:3639–3645. [PubMed: 12393644]
9. Lim ZY, Killick S, Germing U, Cavenagh J, Culligan D, Bacigalupo A, Marsh J, Mufti GJ. Low IPSS score and bone marrow hypocellularity in MDS patients predict hematological responses to antithymocyte globulin. Leukemia. 2007; 21:1436–1441. [PubMed: 17507999]
10. Maciejewski JP, Risitano AM, Sloand EM, Wisch L, Geller N, Barrett JA, Young NS, Ristiano AM. A pilot study of the recombinant soluble human tumour necrosis factor receptor (p75)-Fc fusion protein in patients with myelodysplastic syndrome (erratum appears in Br J Haematol 2002 Jun;117(4):1002 Note: Ristiano Antonio M [corrected to Risitano Antonio M]). British Journal of Haematology. 2002; 117:119–126. [PubMed: 11918541]
11. Molldrem JJ, Caples M, Mavroudis D, Plante M, Young NS, Barrett AJ. Antithymocyte globulin for patients with myelodysplastic syndrome. British Journal of Haematology. 1997; 99:699–705. [PubMed: 9401087]
12. Molldrem JJ, Jiang YZ, Stetler-Stevenson M, Mavroudis D, Hensel N, Barrett AJ. Haematological response of patients with myelodysplastic syndrome to antithymocyte globulin is associated with a loss of lymphocyte-mediated inhibition of CFU-GM and alterations in T-cell receptor Vbeta profiles. British Journal of Haematology. 1998; 102:1314–1322. [PubMed: 9753062]
13. Molldrem JJ, Leifer E, Bahceci E, Saunthararajah Y, Rivera M, Dunbar C, Liu J, Nakamura R, Young NS, Barrett AJ. Antithymocyte globulin for treatment of the bone marrow failure associated with myelodysplastic syndrome [summary for patients in Ann Intern Med. 2002 Aug 6;137(3):1–27]. Annals of Internal Medicine. 2002; 137:156–163. [PubMed: 12160363]
14. Rosenfeld C, Bedell C. Pilot study of recombinant human soluble tumor necrosis factor receptor (TNFR:Fc) in patients with low risk myelodysplastic syndrome. Leukemia Research. 2002; 26:721–724. [PubMed: 12191566]

15. Sauntharajah Y, Nakamura R, Nam JM, Robyn J, Loberiza F, Maciejewski JP, Simonis T, Molldrem J, Young NS, Barrett AJ. HLA-DR15 (DR2) is overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. Blood. 2002; 100:1570–1574. [PubMed: 12176872]
16. Sauntharajah Y, Nakamura R, Wesley R, Wang QJ, Barrett AJ. A simple method to predict response to immunosuppressive therapy in patients with myelodysplastic syndrome. Blood. 2003; 102:3025–3027. [PubMed: 12829603]
17. Sawanobori M, Yamaguchi S, Hasegawa M, Inoue M, Suzuki K, Kamiyama R, Hirokawa K, Kitagawa M. Expression of TNF receptors and related signaling molecules in the bone marrow from patients with myelodysplastic syndromes. Leukemia Research. 2003; 27:583–591. [PubMed: 12681357]
18. Scott BL, Wells DA, Loken MR, Myerson D, Leisenring WM, Deeg HJ. Validation of a flow cytometric scoring system as a prognostic indicator for posttransplantation outcome in patients with myelodysplastic syndrome. Blood. 2008; 112:2681–2686. [PubMed: 18606877]
19. Sloand EM, Wu CO, Greenberg P, Young N, Barrett J. Factors affecting response and survival in patients with myelodysplasia treated with immunosupporessive therapy. Journal of Clinical Oncology. 2008; 26:2505–2511. [PubMed: 18413642]
20. Stadler M, Germing U, Kliche KO, Josten KM, Kuse R, Hofmann WK, Schrezenmeier H, Novotny J, Anders O, Eimermacher H, Verbeek W, Kreipe HH, Heimpel H, Aul C, Ganser A. A prospective, randomised, phase II study of horse antithymocyte globulin vs rabbit antithymocyte globulin as immune-modulating therapy in patients with low-risk myelodysplastic syndromes. Leukemia. 2004; 18:460–465. [PubMed: 14712285]
21. Steensma DP, Dispenzieri A, Moore SB, Schroeder G, Tefferi A. Antithymocyte globulin has limited efficacy and substantial toxicity in unselected anemic patients with myelodysplastic syndrome. Blood. 2003; 101:2156–2158. [PubMed: 12411290]
22. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms (Review). Blood. 2002; 100:2292–2302. [PubMed: 12239137]
23. Yazji S, Giles FJ, Tsimberidou AM, Estey EH, Kantarjian HM, O'Brien SA, Kurzrock R. Antithymocyte globulin (ATG)-based therapy in patients with myelodysplastic syndromes. Leukemia. 2003; 17:2101–2106. [PubMed: 12931212]

Table I

Patient characteristics

No. of patients	25
Age, range (median), ys	53–86 (65)
Gender, M/F, no of patients	19/6
Disease duration, range (median), mos	0.53–115 (17)
WHO stage, no. of patients	
RA	4
RCMD	15
RARS	2
RCMD-RS	3
RAEB-1	1
IPSS risk group, no. of patients	
Low	11
Intermediate-1	14
Cytogenetic Risk Group, no. of patients	
Good	20
Intermediate	4
Poor	1

Table II

IWG responses to ATG / etanercept based on intent to treat.

Response Type	No. of Patients
CR	1
PR	0
Marrow CR	0
Cytogenetic response	0
Erythroid response	13/21*
Platelet response	6/18^
Neutrophil response	2/11#

* 4 patients had a hemoglobin ≥ 11gm/dL at enrollment.

^ 7 patients had a platelet count ≥ 100,000/μL at enrollment.

14 patients had a neutrophil count ≥ 1,000/μL at enrollment.