

Danazol for the Treatment of Myelodysplastic Syndromes: A Systematic Review

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ABSTRACT

Purpose

To study the potential utility of danazol for treating patients with myelodysplastic syndromes, with a focus on efficacy and adverse effects (AEs).

Methods

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus were searched for relevant publications from inception June 1, 1950, until June 28, 2022. The studies were screened by title and abstract, followed by full-text screening. The quality of the included studies was assessed via a prespecified set of questionnaires. Data on the efficacy measures and adverse outcomes were extracted and included in a descriptive summary.

Results

Nine studies consisting of 246 participants were included in our review. The overall quality of the included studies was fair. The age of the participants ranged from 61 to 78 years. In all 9 studies, more male patients had been enrolled than female patients. Overall, a proportion of patients in all the studies reported a desired major response to a danazol dose of 400 to 800 mg/day. Few studies did not observe any improvement in the platelet count. Elevated liver enzyme levels, weight gain, headache, dermatitis, and weakness were the most common AEs observed. One study reported a fatal intracerebral hemorrhage in 1 participant.

Conclusions

Danazol has been effective in increasing platelet count and hemoglobin level. Despite a few AEs, danazol is a safe drug for the treatment of patients with myelodysplastic syndromes.

Myelodysplastic syndromes (MDS) are a group of clonal hematological illnesses defined by inefficient hematopoiesis, varying degrees of peripheral cytopenia, and a propensity to develop acute myeloid leukemia (AML).¹⁻³ There is no pharmacologic treatment to cure MDS. Allogeneic stem cell transplant (ASCT) offers a potential cure rate of 30% to 50%,⁴ but less than 5% of patients are ideal candidates for it. Patients who are not eligible for ASCT have few treatment options.

While a cure for MDS has not yet been found, there have been effective treatments identified to help the population. Azacitidine and decitabine, 2 hypomethylating drugs, have been the first-line therapies advised by the German MDS group for patients with high-risk MDS since 2009.^{5,6} Comparing the use of azacitidine to best supportive care of erythropoietin has shown that the agent reduces the need for transfusions, lessens the risk of developing AML, and ultimately increases survival.⁵ In addition, lenalidomide, a microenvironment-modulating drug, has recently been shown to be a successful treatment, especially for patients with low-risk MDS and deletion 5q.⁶ However, the majority of uninsured patients in low- to middle-income nations are unable to afford these new agents due to their high cost.⁷ In young patients, high-dose chemotherapy may result in complete remission and a notable improvement.⁷

For patients with MDS who are older and have poorer performance status and medical comorbidities, supportive care remains the primary treatment.⁸ Other patient subgroups may respond to growth factors or immunosuppressive medications in varying degrees.⁹

Danazol is a synthetic androgen with progestational and glucocorticoid properties that inhibits the production of tumor necrosis factor α and IL-1.^{10,11} Additionally, danazol has proven useful in immunological cytopenias; its androgenic features, which promote healthy hematopoiesis and decrease neoplastic cell clones, are thought to be responsible for its efficacy.¹¹⁻¹³ One study noted a 5-year overall survival rate of approximately

60% for patients with aplastic anemia treated with danazol.¹⁴

There is, however, conflicting evidence that androgens may be helpful in MDS. Some studies suggest patient benefit, whereas others have demonstrated a lack of efficacy.^{2,8,9,15,16,18-21} Telomere dysfunction as a pathogenic mechanism in various hematological disorders, particularly in bone marrow failure syndromes, has drawn more attention recently.^{22,23} Telomeres are noncoding repeating sequences at the end of each DNA chromosome that help maintain chromosomal stability and prevent chromosomal abnormalities.²⁴

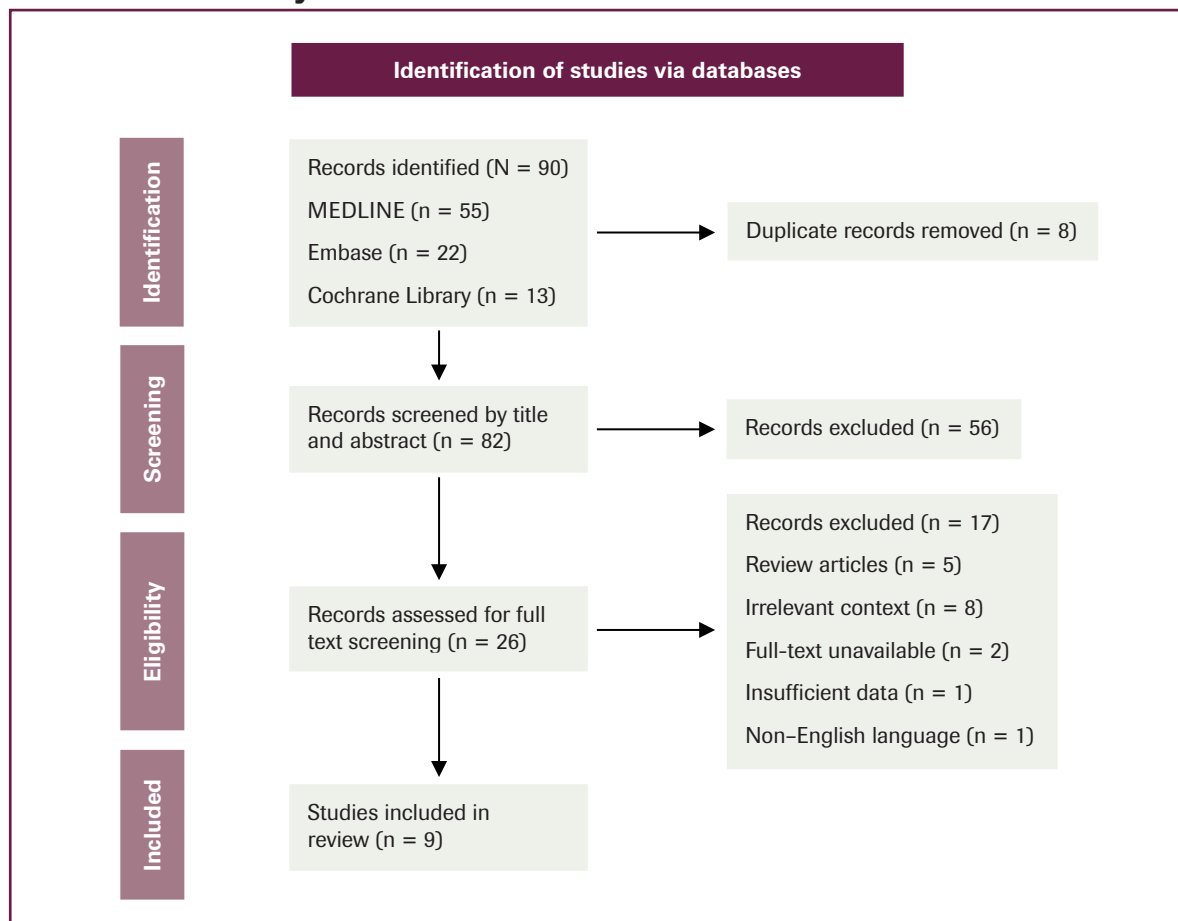
The use of danazol is still a desirable option in a facility with limited access to novel therapeutic alternatives for

patients with MDS, such as hypomethylating drugs and lenalidomide, because of its low cost, local availability, and favorable safety profile. Herein, we systematically review the clinical outcomes of patients diagnosed with MDS and treated with danazol as first-line therapy.

Methods

This study’s protocol was created in advance. The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and its protocol has not been registered in PROSPERO, the international prospective register of systematic reviews.²⁵

FIGURE. PRISMA Study Selection



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

TABLE 1. Quality Assessment of the Included Studies^{2,11,17-20,24-26}

Study	Clarity of study objectives	Study period stated clearly	Criteria for patient selection	Study conducted in multiple centers	Danazol treatment method and dosage mentioned	Baseline equivalence groups clearly considered
Jaime-Pérez et al ¹⁷	1	1	1	1	1	0
Letendre et al ¹⁸	1	1	1	1	1	1
Chan et al ¹¹	1	1	1	1	1	1
Catalano et al ²⁶	1	1	1	1	1	0
Viniou et al ²	1	1	1	1	1	1
Stadtmauer et al ²⁵	1	1	1	1	1	1
Wattel et al ²⁴	1	1	1	1	1	1
Doll et al ¹⁹	1	1	1	1	1	1
Buzaid et al ²⁰	1	1	1	1	1	1

MR, major response; mr, minor response; PC, platelet count.

Data Sources and Search Strategies

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus were all thoroughly searched electronically for relevant pieces of literature published from inception June 1, 1950, until June 28, 2022. The 2 study authors independently planned and carried out the search method. The appendix contains a full description of the search strategy (Supplemental File 1).

Study Selection

Each article’s eligibility was evaluated by 2 separate authors (SS and RY) based on predetermined standards after carefully

reading all the titles and abstracts. We retrieved the pertinent references’ entire texts and uploaded them for full-text evaluation in accordance with the qualifying requirements. Conflicts were settled by consensus and with the help of a third reviewer (KG).

Eligibility Criteria

In this systematic review, we incorporated randomized controlled trials, original papers (cohort, prospective study), and studies that examined the use of danazol to treat patients with MDS. Studies had to report at least 1 of the following outcomes:

- Major response
- Minor response
- Platelet count

According to the study procedures, major response, minor response, increase in platelet count, and hematologic parameters were all defined.

Case reports, editorials, reviews, and articles written in a language other than English were excluded.

Data Extraction

Two reviewers (SS and RY) utilized Microsoft Excel, 2013 version, to create standardized, pilot-tested forms and independently extracted data (2013). Discussions between the 2 reviewers helped settle disagreements. Study characteristics, participant descriptions, intervention information, and important outcomes were retrieved from each study. A number of relevant patient outcomes

TABLE 1. Continued

Definition of primary outcome (MR, mr, or PC) defined prior to the study	Adequate follow-up period	Adverse effects stated	Limitations of each study were considered	Total score
1	1	1	1	9
1	1	1	1	10
1	1	1	1	10
1	1	0	1	8
1	1	0	1	9
1	1	1	1	10
1	1	1	1	10
1	1	1	1	10
1	1	1	1	10
MR, major response; mr, minor response; PC, platelet count.				

Outcome of Interest Efficacy Measures

The following were used to examine patients' functional outcomes:

1. **Major response was defined as:**
 - a more than 2-g/dL increase in hemoglobin level for patients with a pretreatment hemoglobin level of less than 11 g/dL;
 - transfusion independence for patients who were red blood cell (RBC) transfusion dependent;
 - an absolute increase of $30 \times 10^9/L$ or more for patients with a pretreatment platelet count of less than $100 \times 10^9/L$;
 - stabilization of platelet count and platelet transfusion independence for patients who were platelet transfusion dependent; or
 - a 100% increase or an absolute neutrophil count (ANC) increase of more than $0.5 \times 10^9/L$ for patients with a pretreatment ANC of less than $1.5 \times 10^9/L$.

2. **Minor response was defined as:**
 - an increase of 1 to 2 g/dL in hemoglobin level for patients with a pretreatment hemoglobin level of less than 11 g/dL;
 - a 50% decrease in transfusion requirements for patients who were RBC transfusion dependent;
 - a 50% or more increase in platelet count with a net increase greater than $10 \times 10^9/L$ but less than $30 \times 10^9/L$; or
 - an ANC increase of at least 100% but an ANC increase of less than $0.5 \times 10^9/L$.²⁶ Response was required to last at least 2 months.

3. **Increase in platelet count: Response was defined as a platelet count increase of at least $30 \times 10^9/L$.**

were extracted, and we gathered information on the results at the longest follow-up period mentioned in the study.

Quality Assessment

The quality assessment of the included studies was performed by the authors (AB and SS) in accordance with the following items: (1) clarity of the study objectives; (2) study period stated clearly; (3) criteria for patient selection; (4) study conducted in multiple centers; (5) danazol treatment method and dosage mentioned; (6) baseline equivalence groups clearly considered; (7) definition of the primary outcome (major response, minor response, or platelet count defined prior to the study); (8) adequate follow-up period; (9) adverse effects (AEs) stated; and (10) the limitations of each study

were considered. We did not use quality assessment as an exclusion criterion. Individual study questions were answered with *yes* or *no*, with 1 point awarded for *yes* and 0 points for *no*. Total score was calculated for each study. The quality of the included studies was judged to be *fair* (total score, 8-10), *average* (5-7), and *low* (0-4). Consensus with the reviewer (RY) was used to resolve any disputes.

Synthesis of Results

The narrative synopsis with summary tables for attributes covered all identified studies. Additionally, descriptive statistics were used to summarize the data. For dichotomous variables, we used frequencies and percentages, whereas we used mean or median for continuous variables.

TABLE 2. Descriptive Characteristics of the Included Studies^{2,11,17-20,24-26,a}

Study number	Lead author, study year	Sample size	Study design	Country of study	Age (median or mean)	Gender ratio (male:female)	Danazol dose	Efficacy measures	Adverse effects
1	Jaime-Pérez et al, 2017 ¹⁷	42	Retrospective	Mexico	61*	NR	400 mg	•MR •mr	Gastrointestinal symptoms, weight gain
2	Letendre et al, 1995 ¹⁸	46	Prospective	United States	70*	32:14	800 mg	•MR	Dermatitis, exfoliative dermatitis
3	Chan et al, 2002 ¹¹	33	Retrospective	United States	68**	20:13	600 mg, 400 mg, 200 mg	•Increase in PC	Mild headaches, nausea, weight gain
4	Catalano et al, 1993 ²⁶	47	NR	Italy	NR	NR	400-600 mg	•Increase in PC	NR
5	Viniou et al, 200 ²²	17	Prospective	Greece	68**	10:7	600 mg	•Increase in PC	NR
6	Stadtmauer et al, 1991 ²⁵	22	Prospective	United States	65*	14:6	600-800 mg	•Increase in PC	Maculopapular rash, increased serum transaminase level
7	Wattel et al, 1994 ²⁴	13	Prospective	France	61**	8:5	600 mg	•Increase in PC	Weight gain, moderate asthenia, mild liver function test abnormalities
8	Doll et al, 1987 ¹⁹	6	Prospective	United States	72**	5:1	800 mg	•Increase in PC	Suspected exacerbation of thrombocytopenia due to secondary to danazol
9	Buzaid et al, 1987 ²⁰	20	Prospective	United States	68*	4:1	800 mg	•Increase in PC	Headache, mild water retention, transient elevation of liver enzyme levels

MR, molecular response; mr, minimal response; NR, not reported; PC, platelet count.

*median; **mean.

^aThis table includes only the patients we defined in the MR and mr criteria section of this article, so these data may be different from the conclusions published for the individual studies because the response criteria might have been different from ours. We analyzed the charts published with the individual studies to find the data best suited to match our response criteria.

Results

Literature Search and Study Selection

The literature search resulted in the retrieval of 90 studies. After the complete screening process of titles, abstracts, and full texts, 81 studies did not meet the eligibility criteria. Nine articles with various study designs that

met the criteria were included in the review. A description of study selection is shown in the PRISMA flow diagram in the Figure.

Quality Assessment Among the Included Studies

The result of the quality assessment of the included studies is displayed in

Table 1.^{2,11,17-20,24-26} We included and critically analyzed a total of 9 studies, among which 6 scored 10 of 10, 2 scored 9 of 10, and 1 scored 8 of 10. Based on our judgments, all studies scored between 8 and 10 and were therefore deemed *fair* quality. The average score was 9.55, making the overall quality of the included studies *fair*.

TABLE 3. Efficacy Results of the Included Studies^{2,11,17-20,24-26}

Study number	Lead author, study year	Efficacy measure(s)	Outcomes
1	Jaime-Pérez et al, 2017 ¹⁷	1. MR	Sixty percent of patients experienced any response. MR for patients with anemia was 23.8%. MR for ANC was 36.8% and for platelet count was 60%. Median increase in hemoglobin level was 1.1 g/dL (95% CI, 0.7-1.5), in ANC was $0.6 \times 10^9/L$ (95% CI, $0.3-1.1 \times 10^9/L$), and in platelet count was $42 \times 10^9/L$ (95% CI, $16-83 \times 10^9/L$).
		2. Time to initial response	Time to initial response was 2 months; time to best response was 3 months. Median DOR was 6 months. Responders were significantly older than nonresponders (median age 70 vs 52 years, respectively) and had a higher baseline hemoglobin level (9.7 g/dL vs 7.7 g/dL) ($P = .025$ and $P = .009$).
		3. Transfusion independence	Thirteen of 23 patients dependent on transfusion support (57%) became platelet transfusion independent, and 8 of 23 patients dependent on PRBC transfusion support (35%) became independent.
2	Letendre et al, 1995 ¹⁸	MR	One patient improved after danazol treatment, 1 patient had a partial response, and 9 patients had no response (1 nonresponder with an initial neutrophil count of $.7 \times 10^9/L$ did experience a 1-month increase in ANC to $1.5 \times 10^9/L$; another had an increased hemoglobin level of 1 g/dL). Crossover to high dose showed no improvement.
3	Chan et al, 2002 ¹¹	Increase in platelet count	The mean platelet count of participants after 6 weeks of therapy rose to $60 \times 10^9/L$ ($9-223 \times 10^9/L$; $P < .015$); 76% of participants had an increase in platelet count ($1-181 \times 10^9/L$), with 36% of them experiencing a platelet count increase of more than 50%.
4	Catalano et al, 1993 ²⁶	Increase in platelet count	A response was evident in 6 patients who had platelet count increase $> 40 \times 10^9/L$ (in 1 case with an increased WBC count and in 2 cases with discontinuation of the transfusion requirement).
5	Viniou et al, 2002 ²	Increase in platelet count	Platelet antibodies were detected in 70.6% of patients with MDS. Seven patients (41.2%) responded to treatment and achieved a significant increase in platelet count (median value increased from $40 \times 10^9/L$ to $122 \times 10^9/L$).
6	Stadtmauer et al, 1991 ²⁵	Increase in platelet count	Eleven of 22 evaluable patients taking danazol showed improvement of peripheral counts.
7	Wattel et al, 1994 ²⁴	Increase in platelet count	Eight of 13 evaluable patients taking danazol showed improvement of peripheral counts.
8	Doll et al, 1987 ¹⁹	Increase in platelet count	No patient had a response to therapy as determined by an increase in either the hemoglobin level or platelet count, and none of the patients had a prolongation of their transfusion interval.
9	Buzaid et al, 1987 ²⁰	Increase in platelet count	Three patients (15%) responded to the treatment; all responders had an increase in platelet count only.

ANC, absolute neutrophil count; DOR, duration of response; MDS, myelodysplastic syndromes; MR, major response; PRBC, packed red blood cells; WBC, white blood cell.

Descriptive Characteristics of the Included Studies

Nine studies consisting of 246 participants were included in our review. Six were prospective observation studies, and the remaining 4 studies were retrospective. Six studies were performed in North America (5 of which in the United States), and 3 studies were conducted in Europe. The age of the participants ranged from 61 to

72 years, and all 9 studies enrolled more male than female patients. All the studies reported the dose of danazol administered and at least 1 of the efficacy measures (major response, minor response, or increased platelet count). Seven studies reported the AEs of danazol observed in the patients. The descriptive characteristics of the 9 included studies are detailed in **Table 2.**^{2,11,17-20,24-26}

Efficacy Measures

Overall, the participants (with MDS subtypes refractory anemia [RA], RA with ringed sideroblasts [RARS], RA with excess of blasts [RAEB], RAEB in transformation [RAEB-T], or chronic myelomonocytic leukemia [CMML]) in all 9 studies experienced the desired response, and their hemoglobin level and platelet count increased. In studies from which we could derive data, 41.37% of

patients in the RA group, 40% in the CMML group, 35.4% in the RAEB group, 10% in the RAEB-T group, and 4% in RARS group responded with either a major or a minor response. All studies except Buzaid et al followed the participants for 3 months.²⁰

In Catalano et al, 6 of 47 patients who received 400 to 600 mg of daily danazol showed a major response in platelet count and 1 of 47 and 2 of 47 patients showed a major response in ANC and hemoglobin level, respectively.²⁶ Similar results were demonstrated by Chan et al—10 of 33 patients administered 200 to 600 mg of daily danazol showed a major response in platelet count.¹¹ Major responses were satisfactorily obtained in all studies that mentioned it. In the study done by Jaime-Pérez et al, more than half of the participants experienced an increased platelet count.¹⁴ In the study performed by Buzaid et al, all the participants who did not improve had RAEB.²⁰ Stadtmauer et al and Letendre et al both reported an elevated hemoglobin level as the minor response achieved.^{18,25} However, the findings were contrary in Doll et al.¹⁹ None of the participants showed an increased platelet count at a dose of 800 mg/day of danazol. Table 3^{2,11,17-20,24-26} details the outcomes of each study.

Adverse Effects

Elevated liver enzyme levels, weight gain, headache, dermatitis, and weakness were the most common AEs observed among the participants treated with danazol. In Buzaid et al, 2 patients discontinued the drug before 4 weeks, 1 due to a fatal intracerebral hemorrhage and 1 due to intractable headache, which improved after discontinuation of the drug.²⁰ Doll et al¹⁹ reported thrombocytopenia in the participants, but the etiology was not determined and attributed to exacerbation

secondary to danazol administration. The AEs experienced by participants in the included studies are shown in Table 2.

Discussion

Different drugs have been developed to treat patients with MDS, but stem cell transplantation is the only potential cure available; however, there is no cure for the vast majority of patients with MDS.²⁷ As a result, treatment for patients with MDS aims to delay the onset of AML in high-risk patients and reduce cytopenia-related problems in low-risk patients.²⁸

MDS has been treated with corticosteroids, 13-cis-retinoic acid, and androgens with varying degrees of success.^{10,29,30} Hypomethylating drugs have recently been found to improve hematological outcomes in 25% to 50% of patients with high-risk MDS, achieve a full response in 10% to 20% of patients, and enhance survival compared with best supportive therapy.³¹ Despite these hopeful outcomes, 40% to 50% of patients will not benefit from the hypomethylating drugs.³¹ Due to its effectiveness in treating immunological cytopenia, danazol has drawn particular attention. Additionally, it has recently been demonstrated that the agent can lengthen telomeres, resulting in a hematological response in patients with telomere illness.³² However, earlier research on danazol as a treatment for MDS had conflicting outcomes.³²

Since the 1960s, androgens such as danazol have been used to treat MDS and AML.¹⁹ Because clonal myeloid disorders like MDS, AML, and aplastic anemia share anomalies of the *TERC*/*TERT* partners of telomerase activity, one hypothesis for the positive effect of androgens such as danazol on telomerase may explain why norethandrolone has recently been shown to be effective in treating AML.³³

Danazol's mode of action in patients with MDS is still

unknown. Many of our patients' responses took longer than expected, which raises the possibility that the mechanism of action may be immune mediated rather than involving direct stimulation of megakaryocytes. People with idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia respond well to danazol therapy.³⁴ Danazol also has been shown to lower the antiplatelet IgG level in patients with ITP who are responding.^{35,36} A decrease in the quantity of platelet-associated IgG may not be the only mechanism through which the response to danazol is mediated.³⁷ Numerous immunological problems, such as the development of autoantibodies and autoimmune diseases, are linked to MDS,³⁸ and immunosuppressive therapy is effective in certain patients with MDS.³⁹ The delay in platelet response in certain patients after 12 weeks of danazol therapy suggests an immune-mediated impact that may necessitate a prolonged course of treatment, even though danazol's mechanism of action in MDS and immune-mediated illnesses is unknown.

Limitations

Our review had several limitations. First, neither a worse prognosis nor clinical signs were used to choose individuals for the majority of the research. Danazol was used concurrently with other medications, which also affected the results. The efficacy end points that were utilized to measure effectiveness might be unreliable for a variety of MDS. Additionally, the functional scale used to evaluate efficacy varied between studies. The included research also had tiny sample numbers, and the study's time frame was likewise brief. Finally, most of the trials were single center, open label, and nonrandomized.

Conclusions

Our systematic review included a total

of 246 patients; 57 (23.17%) of these patients showed a major response in platelet count, 18 (7.32%) had a major response in ANC, and 15 (6.10%) experienced a major response in hemoglobin level. Two patients showed a minor response in ANC, and 1 patient had a minor response in hemoglobin level. Danazol has been effective in increasing platelet count and hemoglobin level. Despite a few AEs, danazol is a safe treatment option for patients with MDS. ■

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