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Case Reports

Gingival and Oral Mucosal Ulceration Associated with the Myelodysplastic Syndrome

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The features of a patient in whom gingival ulceration was the first symptom of myelodysplasia are detailed.
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INTRODUCTION

THE MYELODYSPLASTIC syndromes are a group of fairly recently recognised haematological disorders characterised by bone marrow hypercellularity, dysplasia of erythrocyte, leucocyte and megakaryocyte cell lines (trilineage dysplasia) and pancytopenia [1]. The type and frequency of oral manifestations is unclear, although there have recently been some reports of hairy leukoplakia [2], oral ulceration [3], Sjogren's-like syndrome [4, 5], oral petechiae, parasthesiae and dysaesthesia [6] and persistent herpes labialis [7].

The present report details the features of a patient whose first presenting manifestation of myelodysplasia was gingival pain and oral ulceration.

CASE REPORT

A 62-year-old male was referred with oral ulceration. The patient suffered from painful ulceration of the right palatal gingivae, right buccal mucosa and right lateral border of tongue for the previous 8 weeks. There was no history of previous oral ulceration and the ulcers had failed to respond to simple measures including 0.2% aqueous chlorhexidine gluconate mouth-rinses and triamicinolone in carboxymethylcellulose paste.

There were no relevant features in the past medical history, and in particular no previous history of gastrointestinal, haematological or dermatological disease. The patient was an office worker, married, with two children and did not smoke tobacco or drink alcohol.

On examination, the only notable extra-oral feature was koilonychia affecting all fingernails but the patient reported this to be congenital. Intra-orally there was a deep 1 cm diameter ulcer of the palatal gingivae (Fig. 1) with similar

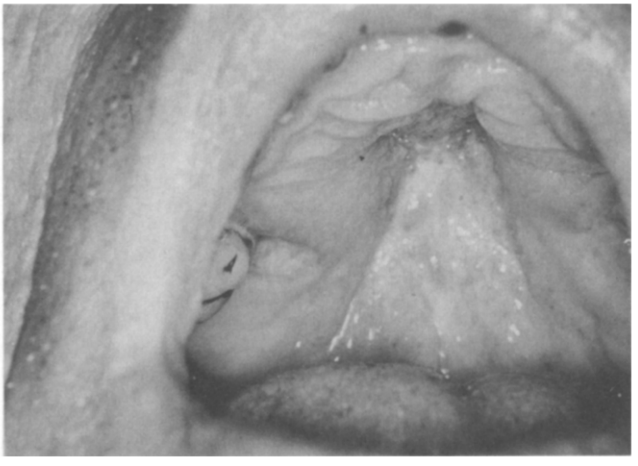

Fig. 1. Ulceration of the palatal gingivae.

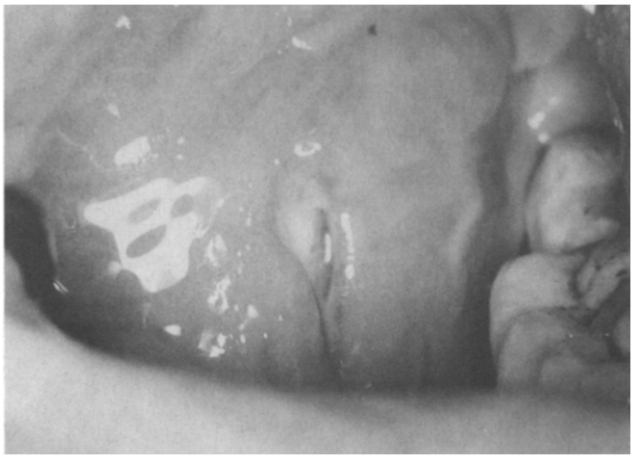

Fig. 2. Chronic ulceration of the right buccal mucosa.

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single ulcers on the right buccal mucosa (Fig. 2) and the right lateral border of tongue. There were no other notable intra-oral features.

A diagnosis of oral ulceration secondary to haematological disease or an inflammatory condition (e.g. syphilis, sarcoidosis) seemed most likely. The oral ulceration was initially treated symptomatically with 0.1% benzydamine hydrochloride spray.

A full blood cell count revealed a pancytopenia (haemoglobin 10.7 g/l, white blood cell count 1.37×10^9/l and platelet count 72×10^9/l) with no evidence of circulating myeloblasts. Levels of red cell folate, and serum levels of vitamin B12, ferritin, hepatic transaminases, alkaline phosphatase, urea, sodium and potassium were all within normal limits. VDRL was negative.

The patient was referred for a haematological opinion and examination of a bone marrow aspiration which showed the marrow to be hypercellular and dysplastic. There was dysplastic and megaloblastic erythopoiesis, grossly dysplastic myelopoiesis with 29% myeloblasts, and some of the megakaryocytes were dysplastic with decreased numbers also present. No ring sideroblasts were present. The diagnosis was thus acute myeloid leukaemia arising from a myelodysplastic bone marrow.

Within 2 weeks of diagnosis blast cells appeared in the peripheral blood and the patient developed painful enlarged, although uninflamed lower anterior gingivae (Fig. 3) which failed to respond to various agents prescribed by haematology staff, including fluconazole, ciprofloxacin, acyclovir or metronidazole. The pancytopenia was so extreme that, by 5 weeks after diagnosis the patient needed regular blood transfusions. He is currently receiving cytotoxic chemotherapy as recent bone marrow trephine biopsy indicated that most of the myeloid tissue consisted of myeloblasts. The oral ulceration is now controlled by chlorhexidine gluconate mouth-rinse.

DISCUSSION

The myelodysplastic syndromes (MDS) are characterised by hypercellular bone marrow, trilineage dysplasia and peripheral pancytopenia [1]. MDS can anticipate the onset of acute leukaemia and thus have been described as primary preleukaemias in contrast to secondary preleukaemic disorders such as Fanconi's anaemia, Bloom's syndrome, ataxia telangiectasia and Down's syndrome in which there are chromosomal anomalies and an increased risk of acute leukaemia.

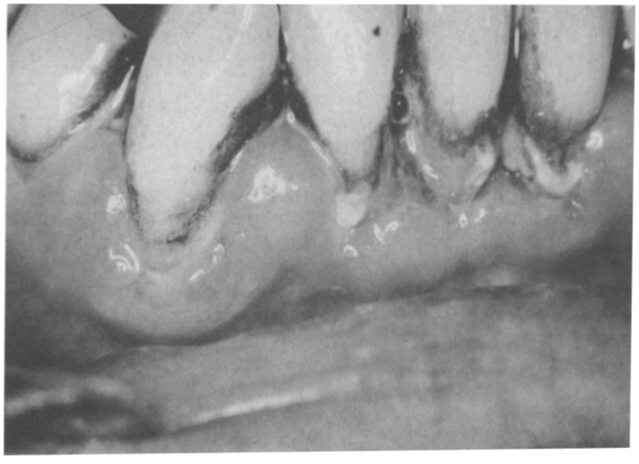

Fig. 3. Non-inflammatory gingival enlargement associated with acute myeloid leukaemia arising from myelodysplasia.

The MDS are a group of heterogeneous disorders whose classification is based upon morphological features of cells in the peripheral blood film and bone marrow biopsy (Table 1) [8]. Other disorders which may give rise to similar cellular changes including cytotoxic drug therapy [9–11], untreated megaloblastic anaemia [12], HIV-disease [13] or paraneoplastic phenomena, but these are aetiologically distinct from MDS. In addition, there are a variety of other morphological and functional cellular abnormalities in the bone marrow and peripheral blood (Table 2) [14].

Patients with MDS are usually middle-aged to elderly and have symptoms and signs that reflect bone marrow failure—that is lethargy, liability to bacterial and fungal infections, epistaxis, and easy bruising. Fever without overt infection is not infrequent [15]. Occasional associations include urticaria pigmentosa [16], pyoderma gangrenosum [17], relapsing polychrondritis [18], lymphoid and plasmacytic neoplasms [19], non-haematological malignancies [20], autoimmune phenomena [21], myelofibrosis [22], Sweet's syndrome (neutrophilic dermatosis) [23], cutaneous vasculitides, neuropathies and lupoid syndrome.

There is a significant risk of transformation of MDS to acute myeloid leukaemia (AML) particularly in those patients with refractory anaemia with excess blasts in transformation (RAEBt) (Table 1), as in the present patient. However, as a result of marrow failure there is significant morbidity and mortality even in the absence of transformation to AML. Indeed, more than half of the patients with MDS succumb within 1 year of diagnosis [10].

MDS probably occurs as a result of the proliferation of a genetically unstable clone of haemopoietic stem cells followed by the appearance of chromosomal abnormalities in a subclone which then gains functional ascendency [24]. Approximately 40–80% of patients with MDS have clonal cytogenetic abnormalities of which partial deletion of the long arm of chromosome 5 (5q−), trisomy 8 (+8) and monosomy or partial deletion of chromosome 7 (−7 or 7q−) are the most frequent [25–28]. There is no clear association between particular cytogenetic abnormalities and specific types of MDS, but chromosomal abnormalities are most frequent in the RAEB and RAEBt types. Single or multiple abnormalities of chromosome 7 or 8, or chromosome abnormality appearing in a patient with a previously normal karyotype are poor prognostic features. Of patients with MDS, 9–41% have mutant *ras* genes, 80% occurring in N-*ras*, 17% in K-*ras* and 3% in H-*ras* [29–33]. Mutant *ras* genes may occur in all types of MDS and their presence is associated with earlier leukaemic transformation and a shorter survival [29–31].

Therapy of MDS depends on the particular type of MDS (Table 1). Patients with MDS types RA and RAS may need little therapy other than correction of any underlying haematinic deficiency or thrombocytopenia and/or neutropenia, and the last two groups may only require occasional blood transfusion [15]. Agents such as corticosteroids [34] or androgenic steroids [35] are of little value. BCG inoculations [36], lithium salts [37], danazol [38], granulocyte–macrophage colony-stimulating factor (GM-CSF) [39–44], granulocyte colony-stimulating factor [45–47], retinoids [48–52] and interferons [53–55] have been used to variable effect. Where acute myeloid leukaemia appears, intensive chemotherapy

Table 1. French American British (FAB) classification of myelodysplastic syndromes

Type	Blood film	Bone marrow biopsy
Refractory anaemia (RA)	<1% blasts	Dysplasia in one or more lineage <5% blasts
RA with ring sideroblasts (RAS)	<1% blasts	As RA with ring sideroblasts representing at least 15% erythroblasts
RA with excess of blasts (RAEB)	<5% blasts	As RA with 5–20% blasts
RAEB in transformation (RAEBt)	As RAEB but with 5% blasts or with Auer rods	As RA with 20–30% blasts or as RAEB with Auer rods
Chronic myelomonocytic leukaemia (CMML)	As any of the above, with $>1 \times 10^9$/l monocytes	As any of the above plus promonocytes

Table 2. Morphological and functional abnormalities in myelodysplastic syndromes

Cell line	Blood	Bone marrow
Erythrocytes	Anisocytosis and poikilocytosis; macrocytes, ovalocytes, hypochromatic or stippled cells, nucleated red cells	Nuclear budding, megaloblasts, multinuclear erythroblasts, sideroblasts, PAS positivity
	Enzyme defects, cell surface antigen changes, PNH-like lesions, haemoglobin F, acquired HbH	
Leukocytes	Nuclear blebs, hyposegmentation ("Pelger" anomaly), giant lobes, hypersegmentation, nuclear clumping, atypical monocytes	Maturation arrest, atypical blast and mononuclear cells ("paramyeloid" cells), abnormal or deficient granulation, vacuolation
	Reduced bacteriocidal, chemotactic and phagocytic activity	Reduced myeloperoxidase, chloracetate and alkaline phosphatase activity
Thrombocytes	Giant forms deficient in granules, membrane abnormalities	Giant or micromegakaryocytes
	Abnormal platelet adhesion and aggregation, prolonged bleeding time	

may be indicated, but the advanced age of most affected patients often renders this inappropriate [15]. Remission is often not achieved or is only of short duration. Single agent chemotherapy using cytosine arabinoside, hydroxyurea, etoposide, mercaptopurine or busulfan may be used [56]. Low dose cytosine arabinoside can be of benefit but results are unpredictable, and bone marrow hypoplasia can occur [14, 57–59]. Newer therapies such as 5-azacytidine [60] or 5-aza-2′-deoxycitidine [61] may cause less bone marrow hypoplasia but these agents require further study.

In young patients with progressive MDS, those with life-threatening cytopenia, and those with cytogenetic abnormalities associated with a poor prognosis, bone marrow transplantation (BMT) is the treatment of first choice. Over 45% can go into remission and remain well for up to 215 months after BMT [62–67]. Relapse after BMT is highest in those with the RAEB and RAEBt types of MDS [68].

Indicators of poor prognosis include rapid increase in marrow blasts, old age, severe anaemia, granulocytopenia and thrombocytopenia [69, 70], and where there is abnormal localisation of immature precursors (ALIP) in the bone marrow intestine [71], complex cytogenetic abnormalities, or the development of organomegaly [72].

In summary, the oral features of a patient with myelodysplastic syndrome have been described. The patient had oral and gingival ulceration as the initial clinical features of the RAEBt type of myelodysplatic syndrome and, as acute myeloid leukaemia evolved, he also developed gingival pain and enlargement. The myelodysplatic disorders are another group of haematological malignancies that can give rise to oral problems, particularly ulceration.

1. Lichtman MA, Brennan JK. Preleukemia and oligoblastic leukemia (myelodysplatic disorders). In Williams WJ, Beutler E, Erskv AJ, Lichtman MA, eds. *Haematology* 4th edition. New York, McGraw-Hill Publishing Company, 1990, 175–187.
2. Ficcara G, Mitiani A, Adler-Storthz K, *et al.* Recurrent londyloma acuminat and hairy leukoplakia: an early sign of myelodysplastic syndrome in an HIVseronegative patient, *J Oral Pathol Med* 1991, **20**, 398.
3. Epstein JB, Priddy RW, Sparling T, Wadsworth L. Oral manifestations in myelodysplastic syndrome. *Oral Surg Oral Med Oral Pathol* 1986, **61**, 466–470.
4. Vrielinck LJG, van Parys G, van Damme B, Bossuyt M. Sicca syndrome with iron deposition in the salivary glands. *Int J Oral Maxillofac Surg* 1988, **17**, 11–13.
5. Castro M, Doyt L, Conn WP, Daniel S, Garton JP. Rheumatic manifestations in myelodysplastic syndromes. *J Rheumatol* 1991, **18**, 721–727.
6. Gibson J, Lamey P-J, Watson WH, Tansey P. The myelodysplastic syndrome presenting with oral symptoms. *Br Dent J* 1987, **163**, 234–235.
7. Flint SR, Sugarman P, Scully C, Smith RG, Smith MA. The myelodysplastic syndromes. *Oral Surg Oral Med Oral Pathol* 1990, **70**, 579–583.
8. Bennett JM, Catovsky D, Daniel MT. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol* 1982, **51**, 189–199.

9. Michels SD, McKenna RW, Arthur DC, *et al.* Therapy related acute myeloid leukemia and myelodysplastic syndromes: a clinical and morphological study of 65 cases. *Blood* 1985, **65**, 1364–1372.
10. Kantarijan HM, Keating MJ, Walters RS, *et al.* Therapy related leukaemia and myelodysplastic syndrome: clinical, cytogenetic and prognostic features. *J Clin Oncol* 1986, **4**, 1748–1757.
11. Bennett JM, Moloney WC, Greene MH, *et al.* Acute myeloid leukaemia and other myelopathic disorders following treatment with alkylating agents. *Haematol Pathol* 1987, **1**, 99–104.
12. Dokal IS, Cox TM, Galton DAG. Vitamin B12 and folate deficiency presenting as leukaemia. *Br Med J* 1990, **300**, 1263–1264.
13. Costello C. Haematological abnormalities in human immunodeficiency virus (HIV) disease. *J Clin Pathol* 1988, **41**, 711–715.
14. Mufti GJ. Myelodysplastic syndromes. In Lawson DH, ed. *Current Medicine* 2. Edinburgh, Churchill Livingstone, 1990, 119–136.
15. Geary CG, Macheta AT. Preleukaemia and myelodysplasia: morphology, clinical presentation and treatment. In Whittaker JA, ed. *Leukaemia* 2nd edn. London, Blackwell Scientific Publications, 1992, 509–540.
16. Vilter RW, Wiltse D. Preleukaemia and urticaria pigmentosa followed by acute myelomonoblastic leukaemia. *Arch Intern Med* 1985, **145**, 349–352.
17. Jacobs P, Palmer S, Gordon-Smith EC. Pyoderma gangrenosum in myelodysplasia and acute leukaemia. *Postgrad Med J* 1985, **61**, 689–694.
18. Michet JC, McKenna CH, Luthra HS, O'Fallon WM. Relapsing polychondritis. Survival and predictive role of early disease manifestations. *Ann Intern Med* 1986, **104**, 74–78.
19. Copplestone JA, Mufti GJ, Hamblin TJ, Oscier DG. Immunological abnormalities in myelodysplastic syndromes. II. Coexistent lymphoid or plasma cell neoplasms: a report of 20 cases unrelated to chemotherapy. *Br J Haematol* 1986, **63**, 149–159.
20. Layton DM, Mufti GJ. The myelodysplastic syndromes. *Br Med J* 1987, **295**, 227–228.
21. Mufti GJ, Figes A, Hamblin TJ, Oscier DG, Copplestone JA. Immunological abnormalities in myelodysplastic syndromes. I. Serum immunoglobulins and autoantibodies. *Br J Haematol* 1986, **63**, 143–147.
22. Pagliuca A, Layton DM, Manoharan A, Gordon S, Green PJ, Mufti GJ. Myelofibrosis in primary myelodysplastic syndromes: a clinico-morphological study of 10 cases [Abstract]. *Br J Haematol* 1989, **71**, 499–504.
23. Soppi E, Nousiainen T, Seppa A, Lahtinen R. Acute febrile neutrophilic dermatosis (Sweet's syndrome) in association with myelodysplastic syndromes: A report of three cases and a review of the literature. *Br J Haematol* 1989, **73**, 43–47.
24. Jacobs A, Culligan D. Myelodysplasia and preleukaemia: pathogenesis and functional aspects. In Whittaker JA, ed. *Leukaemia* 2nd edn. London, Blackwell Scientific, 1992, 227–250.
25. Machnicki JL, Bloomfield CD. Chromosomal abnormalities in myelodysplastic syndromes and acute myeloid leukemia. *Clin Lab Med* 1990, **10**, 755–767.
26. Jotterand-Bellomo M, Parlier V, Schmidt PM, Beris PH. Results of chromosome studies and their relation to morphology, course, and prognosis of 120 patients with de novo myelodysplastic syndrome. *Cancer Genet Cytogenet* 1990, **44**, 15–26.
27. List AF, Garweal HS, Sandberg AA. The myelodysplastic syndromes: biology and implications for management. *J Clin Oncol* 1990, **8**, 1424–1441.
28. Nowell PC, Besa EC. Prognostic significance of single chromosome abnormalities in preleukemic states. *Cancer Genet Cytogenet* 1989, **42**, 1–7.
29. Liu ET. The role of *ras* gene mutations in myeloproliferative disorders. *Clin Lab Med* 1990, **10**, 797–807.
30. Lyon J, Janssen JWG, Bartram C, Layton M, Mufti GJ. Mutation of Ki-*ras* and N-*ras* oncogenes in myelodysplastic syndromes. *Blood* 1988, **71**, 1707–1712.
31. Yunis JI, Boot AJM, Mayer MG, Bos JL. Mechanisms of *ras* mutation in myelodysplastic syndrome. *Leuk Res* 1989, **4**, 609–614.
32. Melani C, Haliassos A, Chomel JC, *et al. Ras* activation in myelodysplastic syndromes: clinical and molecular study of the chronic phase of the disease. *Br J Haematol* 1990, **74**, 408–413.
33. Bar-Eli M, Ahuja H, Gonzalez-Cadavid N, Foti A, Cline MJ. Analysis of N-*ras* exon-1 mutations in myelodysplatic syndromes by polymerase chain reaction and direct sequencing. *Blood* 1989, **73**, 281–283.
34. Bagby GC Jr, Gabourel JD, Linman JW. Glucocorticoid therapy in the preleukaemic syndrome (haemopoietic dysplasia). *Ann Intern Med* 1980, **92**, 55–58.
35. Najean Y, Pecking A. Refractory anaemia with exess of blast cells; prognostic factors and effect of treatment with androgens or cystosine arabinoside, results of a prospective trial in 58 patients. *Cancer* 1979, **44**, 1976–1982.
36. Hast R, Bevan M, Reizenstein P. Studies on human preleukaemia. VI. Non-specific immunotherapy (BCG) in five patients with a regenerative anaemia and hypercellular bone marrow. In Schmalzl F, Hellriegel K-P, eds. *Preleukaemia*. Berlin, Springer Verlag, 1979, 170–173.
37. Buzaid AC, Garewal HS, Greenberg BR. Management of myelodysplastic syndromes. *Am J Haematol* 1966, **80**, 1149–1157.
38. Cines DB, Cassileth PA, Kiss JE. Danazol therapy in myelodysplasia. *Ann Intern Med* 1985, **103**, 58.
39. Antin JH, Smith BR, Holmes W, Rosenthal DS. Phase I/II study of recombinant human granulocyte macrophage colony stimulating factor in aplastic anaemia and myelodysplastic syndrome. *Blood* 1988, **72**, 705–710.
40. Ganser A, Volkers B, Greher J, *et al.* Recombinant human granulocytic-macrophage colony stimulating factor in patients with myelodysplastic syndromes in phase I/II trial. *Blood* 1989, **73**, 31–36.
41. Thompson JA, Lee DJ, Kidd P, Rubin E, Kaufmann J, Bonnem EM, Fefer A. Subcutaneous granulocyte–macrophage colony-stimulating factor in patients with myelodysplastic syndrome: toxicity, pharmacokinetics, and hematological effects. *J Clin Oncol* 1989, **7**, 629–637.
42. Herrmann F, Lindmann A, Klein H, Lubbert M, Schultz G, Mertelsmann R. Effect of recombinant human granulocyte-macrophage colony-stimulating factor in patients with myelodysplastic syndrome with excess blasts. *Leukemia* 1989, **3**, 335–339.
43. Vadhan-Raj S, Broxmeyer HE, Spitzer G, *et al.* Stimulation of non-clonal hematopoiesis and suppression of the neoplastic clone after treatment with recombinant human granulocyte-macrophage colony stimulating factor in a patient with therapy related myelodysplastic syndrome. *Blood* 1989, **74**, 1491–1498.
44. Schuster MW, Larson RA, Thompson JA, Coiffier B, Bennett JM, Israel RJ, for the Schering-Plough Sandoz MDS Study Group. Granulocyte–macrophage colony stimulating factor (GM-CSF) for myelodysplastic syndrome (MDS): results of a multi-center randomized controlled trial (abstract). *Blood* 1990, **76** (suppl 1), 318a.
45. Nagler A, Binet C, Mackichan ML *et al.* Impact of marrow cytogenetics and morphology on *in vitro* hematopoiesis in the myelodysplastic syndromes: comparison between recombinant human granulocyte colony-stimulating factor (CSF) and granulocyte–monocyte CSF. *Blood* 1990, **76**, 1299–1307.
46. Nagler A, Ginzton N, Negrin R, Bang D, Donlon T, Greenberg P. Effects of recombinant human granulocyte colony stimulating factor and granulocyte-monocyte colony stimulating factor on *in vitro* hematopoiesis in the myelodysplastic syndromes. *Leukemia* 1990, **4**, 193–202.
47. Kobayashi Y, Okabe T, Ozawa K, *et al.* Treatment of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor: a preliminary report. *Am J Med* 1989, **86**, 178–182.
48. Gold EJ, Mertelsmann RH, Itri LM, *et al.* Phase 1 clinical trial of 13-*cis*-retinoic acid in myelodysplastic syndromes. *Cancer Treatment Reports* 1983, **67**, 981–986.
49. Clark RE, Lush CJ, Smith SA, *et al.* Effect of 13-*cis* retinoic acid on survival of patients with myelodysplastic syndrome. *Lancet* 1987, **i**, 763–765.
50. Clark RE, Ismail SA, Jacobs A, *et al.* A randomised trial of 13-*cis* retinoic acid with or without cytosine arabinoside in patients with the myelodysplastic syndrome. *Br J Haematol* 1987, **66**, 77–83.
51. Koeffler HP, Heitjan D, Merteismann R, *et al.* A randomised study of 13-*cis* retinoic acid V placebo in the myelodysplastic disorders. *Blood* 1988, **71**, 703–708.
52. Besa EC, Abraham JL, Bartholomew MJ, Hyzinski M, Nowell PC. Treatment with 13-*cis*-retinoic acid in transfusion-dependent patients with myelodysplastic syndrome and decreased toxicity with addition of α-tocopherol. *Am J Med* 1990, **89**, 739–747.
53. Gisslinger H, Chott A, Linkesch W, Fritz E, Ludwig H. Long-

term alpha-interferon therapy in myelodysplastic syndromes. *Leukemia* 1990, **4**, 91–94.
54. Schwarzinger H, Stain CB, Ettelheim P, Hinterberger W, Lechner K. Gamma-interferon in myelodysplastic syndromes: a pilot study. *Oncology* 1990, **47**, 322–326.
55. Maiolo AT, Cortelezzi A, Calori R, Polli EE. Recombinant gamma-interferon as first line therapy for high risk myelodysplastic syndromes. *Leukemia* 1990, **4**, 480–485.
56. Hamblin TJ, Oscier PG. The myelodysplastic syndromes: a practical guide. *Haematol Oncol* 1987, **5**, 19–34.
57. Cheson BD, Jasperse DM, Simo R, Friedman MA. A critical appraisal of low dose cytosine arabinoside in patients with acute non-lymphocytic leukaemia and myelodysplastic syndromes. *J Clin Oncol* 1986, **4**, 1857–1864.
58. Cheson BD. The myelodysplastic syndromes: current approaches to therapy. *Ann Intern Med* 1990, **112**, 932–941.
59. Cheson BD, Simon R. Low-dose ara-C in acute nonlymphocytic leukemia and myelodysplastic syndromes: a review of 20 years' experience. *Semin Oncol* 1987, **14** (suppl 1), 126–133.
60. Silverman LR, Davis RB, Holland JF, *et al.* 5-azacytidine (AZ) as a low dose continuous infusion is an effective therapy for patients with myelodysplastic syndromes (MDS). *Proc Am Soc Clin Oncol* 1989, **8**, 198.
61. Pinto A, Zagonel V, Attadia V, *et al.* 5-aza-2'-deoxycitidine as a differentiation inducer in acute myeloid leukaemias and myelodysplastic syndromes of the elderly. *Bone Marrow Transplant* 1989, **4** (suppl 3), 28–32.
62. Appelbaum FR, Storb R, Ranberg RE, *et al.* Treatment of preleukaemic syndromes with marrow transplantation. *Blood* 1987, **69**, 92–96.
63. O'Donnel MR, Nademanee AP, Snyder DS, *et al.* Bone marrow transplantation for myelodysplastic and myeloproliferative syndromes. *J Clin Oncol* 1987, **5**, 1822.
64. Belanger R, Gyger M, Peneault C, *et al.* Bone marrow transplantation for myelodysplastic syndromes. *Br J Haematol* 1988, **69**, 29–33.
65. Tricot G, Van Hoof A, Zachee P, *et al.* Bone marrow transplantation performed as first-time treatment in two cases of secondary acute leukaemia. *Leukemia Res* 1984, **8**, 93–96.
66. De Witte T, Zwaan F, Hermans J, *et al.* Allogeneic bone marrow transplantation for secondary leukaemia and myelodysplastic syndrome. Survey by Leukaemia Working Party of European Bone Marrow Transplantation Group (EBMTG). *Br J Haematol* 1990, **74**, 151–155.
67. Longmore G, Guinan EC, Weinstein HJ, Gelber RD, Rappeport JM, Antin JH. Bone marrow transplantation for myelodysplasia and secondary acute nonlymphoblastic leukemia. *J Clin Oncol* 1990, **8**, 1707–1714.
68. Heyman MR. Recent advances in biology and treatment of myelodysplasia. *Curr Opin Oncol* 1991, **3**, 44–53.
69. Greenberg PL. The smouldering myeloid leukemic states: clinical and biological features. *Blood* 1983, **61**, 1035–1044.
70. Weisdorf DJ, Oken MM, Johnson GT, *et al.* Chronic myelodysplastic syndromes. Short survival with or without evolution to acute leukaemia. *Br J Haematol* 1983, **55**, 691–700.
71. Tricot G, De Wolf-Peeters C, Vlietoinck R, *et al.* Bone marrow histology in myelodysplastic syndromes. II. Prognostic value of abnormal localisation of immature precursors in MDS. *Br J Haematol* 1984, **58**, 217–225.
72. Cohen JR, Gregor WP, Greenberg PL, *et al.* Subacute myeloid leukemia. *Am J Med* 1979, **66**, 959–966.