type I. Blood 1996;87:1763-70.
3. Wickramasinghe SN, Thein SL, Srichairatanakool S, Porter JB. Determinants of iron status and bilirubin levels in congenital dyserythropoietic anaemia type 1. Br J Haematol 1999;107:522-5.
4. Wickramasinghe SN. Congenital dyserythropoietic anaemias: clinical features, haematological morphology and new biochemical data. Blood Reviews 1998;12:178-200.
5. Wickramasinghe SN. Congenital dyserythropoietic anemias. In: Blood and Bone Marrow Pathology: eds. Wickramasinghe SN and McCullough J. Churchill Livingstone, Elsevier Science, 2003, pp. 273-82.
6. Tamary H, Shalev H, Perez-Avraham G, Zoldan M, Levi I, Swinkels DW, et al. Elevated growth differentiation factor 15 expression in patients with congenital dyserythropoietic anemia type I. Blood 2008;112:5241-4.
7. Shalev H, Moser A, Kapelushnik J, Karplus M, Zucker N, Yaniv I, Tamary H. Congenital dyserythropoietic anemia type I presenting as persistent pulmonary hypertension of the newborn. J Pediat 2000;136:553-5.
8. Tamary H, Offret H, Dgany O, Foliguet O, Wickramasinghe SN, Krasnov T, et al. Congenital dyserythropoietic anaemia, type I, in a Caucasian patient with retinal angioid streaks (homozygous arg1042trp mutation in codanin-1). Eur J Haematol 2008;80:271-4.
9. Heimpel H, Schwarz K, Ebnöther M, Goede JS, Heydrich D, Kamp T, et al. Congenital dyserythropoietic anaemia type I (CDA I): molecular genetics, clinical appearance, and prognosis based on long-term observation. Blood 2006; 107:334-40.
10. Lavabre-Bertrand T, Ramos J, Delfour C, Henry L, Guiraud I, Carillo S, et al. Long term alpha interferon treatment is effective on anaemia and significantly reduces iron overload in congenital dyserythropoiesis type I. Eur J Haematol 2004;73:380-3.
11. Remacha AF, Badell I, Pujol-Moix N, Parra J, Muñiz-Diaz E, Ginovart G, et al. Hydrops fetalis associated congenital dyserythropoietic anemia treated with intrauterine transfusions and bone marrow transplantation. Blood 2002;100: 356-8.
12. Tamary H, Shalmon L, Shalev H, Halil A, Dobrushin D, Ashkenazi N, et al. Localisation of the gene for congenital dyserythropietic anemia type I to a chromosome <1-cM interval on chromosome 15q15.1-15.3. Am J Hum Genet 1998;62:1062-9.
13. Dgany O, Avidan N, Delaunay J, Krasnov T, Shalmon L, Shalev H, et al. Congenital dyserythropoietic anemia type I is caused by mutations in codanin-1. Am J Human Genet 2002;71:1467-74.
14. Tamary H, Dgany O, Proust A, Krasnov T, Avidan N, Eidelitz-Markus T, et al. Clinical and molecular variability in congenital dyserythropoietic anaemia type I. Br J Haematol 2005;130:625-34.
15. Hodges VV, Molloy GY, Wickramasinghe SN. Genetic heterogeneity of congenital dyserythropoietic anemia. Blood 1999;94:1139-40.
16. Ahmed MR, Chehal A, Zahed L, Taher A, Haidar J, Shamseddine A, et al. Linkage and mutational analysis of the CDAN1 gene reveals genetic heterogeneity in congenital dyserythropoietic anemia type I. Blood 2006;107:4968-9.
17. Avidan N, Tamary H, Dgany O, Cattan D, Pariente A, Thulliez M, et al. CatSper2, a human autosomal non-syndromic male infertility gene. Eur J Hum Genet 2003;11:497-502.
18. Gasparini P, Miraglia del Giudice E, Delaunay J, Totaro A, Granatiero M, Melchionda S, et al. Localization of the congenital dyserythropoietic anemia II locus to chromosome 20q11.2 by genomewide search. Am J Hum Genet 1997; 61:1112-6.
19. Iolascon A, Servedio V, Carbone R, Totaro A, Carella M, Perrotta S, et al. Geographic distribution of CDA-II: did a founder effect operate in Southern Italy? Haematologica 2000;85:470-4.
20. Iolascon A, Delaunay J, Wickramasinghe SN, Perrotta S, Gigante M, Camaschella C. Natural history of congenital dyserythropoietic anemia type II. Blood 2001;98:1258-60.
21. Alloisio N, Texier P, Denoroy L, Berger C, Miraglia del Giudice E, Perrotta S, et al. The cisternae decorating the red blood cell membrane in congenital dyserythropoietic anemia (type II) originate from the endoplasmic reticulum. Blood 1996;87:4433-9.
22. Zdebska E, Iolascon A, Spychalska J, Perrotta S, Lanzara C, Smolenska-Sym G, Koscielak J. Abnormalities of erythrocyte glycoconjugates are identical in two families with congenital dyserythropoietic anemia type II with different chromosomal localizations of the disease gene. Haematologica 2007;92:427-8.
23. De Franceschi L, Turrini F, Miraglia del Giudice E, Perrotta S, Olivieri O, Corrocher R, et al. Decreased band 3 anion transport activity and band 3 clusterization in congenital dyserythropoietic anemia type II. Exp Hematol 1998;26: 869-73.
24. Perrotta S, Luzzatto L, Carella M, Iolascon A. Congenital dyserythropoietic anaemia type II in human patients is not due to mutations in erythroid anion exchanger 1. Blood 2003;102:2704-5.
25. Lanzara C, Ficarella R, Totaro A, Chen X, Roberto R, Perrotta S, et al. Congenital dyserythropoietic anemia type II: exclusion of seven candidate genes. Blood Cells Mol Dis 2003;30:22-9.
26. Nichols KE, Crispino JD, Poncz M, White JG, Orkin SH, Maris JM, et al. Familial dyserythropoietic anaemia and thrombocytopenia due to an inherited mutation in GATA1. Nat Genet 2000;24:266-70.

Clinical relevance of extra-hematologic comorbidity in the management of patients with myelodysplastic syndrome

Matteo Giovanni Della Porta and Luca Malcovati

Department of Hematology and Oncology, University of Pavia Medical School, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy. E-mail: mg.dallaporta@haematologica.org. *doi:10.3324/haematol.2009.005702*

Malignancies have an increasing incidence with age. At present, 60% of cancers and two-thirds of cancer deaths occur over the age of 65 years in developed countries. This proportion is expected to increase markedly in the next decades as a consequence of the ageing of the population.[1]

One aspect of ageing is an increased prevalence of comorbidity. In a typical geriatric population, subjects aged 65 years and older suffer on average from three or more concomitant diseases. Similarly, older patients with malignancy present a high prevalence of comorbidity.[2] As a result, hematologists and oncologists will increasingly treat patients who have concomitant diseases.

Comorbidity is recognized to have an unfavorable effect on life expectancy of patients with cancer, as well as to influence clinical decision making. There is a negative clinical effect *per se* in terms of competing risk of death with primary disease. Furthermore, presence of comorbidity significantly affects therapeutic strategies,

being a major reason of undertreatment of patients. Finally, several studies showed that cancer patients with comorbidity have reduced tolerance to treatment and higher risk of complications, possibly resulting in a worse post-therapeutic outcome.[3,4]

The evaluation of the influence of comorbidity in cancer patients is made complex by many critical issues. The first important point to be considered is that, so far, clinical trials have provided little information on comorbidity. In fact, in only 20-40% of phase II and III studies are patients aged 65 years or older.[5] As a consequence, clinicians are provided with a weak base of evidence when applying the results of these clinical investigations to patients with comorbidity. Therefore efforts aimed to integrate comorbidity in clinical studies and to promote the design of clinical trials focused on older patients are warranted.

The second source of complexity consists in developing reliable tools to measure comorbidity and its effect on outcome.[6] Available measures can be divided into two groups: general measures intended for use in general patient populations, and disease-specific measures.

The most commonly used general comorbidity measure is the Charlson Comorbidity Index (CCI).[7] It was developed to predict 1-year mortality in medical inpatients. Nineteen comorbid conditions are assigned weights based on the ratio of the mortality risk for patients with the comorbidity of interest versus the mortality risk for those without. The index was validated in a cohort of breast cancer patients, with the 10-year mortality rate as an endpoint. The CCI is widely used, has a good inter-rater and test-retest reliability, and predicts mortality in different clinical conditions. One weakness of these general tools is the assumption that each comorbidity computed in the measure has the same impact in different diseases and patient populations. In addition, they may include conditions that are complications of the major underlying disease rather than independent clinical entities, and generally do not account for the severity of the comorbidity, which may strongly affect the outcome.

These limitations may be particularly relevant in patients with malignancies. In fact, for any given cancer, different comorbid conditions may have different effects. In addition the prognostic impact of a comorbidity may vary across types of malignancy and treatments, and may affect cancer care at multiple steps.[3]

Disease-specific comorbidity measures are developed and tested in a single disease population, and intended for use only in that setting.[8] They have a conceptual advantage in that they account for specific treatments and outcomes unique to the population of interest.[6]

A major limitation in implementing either general or disease-specific measures is the data source used for their generation. Clinical trials that include detailed prospective information about patients and treatments are theoretically the best data sets to evaluate the impact of comorbid conditions. However, only a minority of all adult cancer patients are enrolled and the results cannot be easily applied to the general patient population.[5] Cancer-specific registries provide the opportunity to collect information on comorbidity and self-reported outcomes from a more representative patient sample.[1] However, such a systematic data collection is extremely demanding, and available only in a minority of clinical settings. In the light of these drawbacks, retrospective studies, despite potential biases related to data recording, represent a valuable source of information, which is relatively accessible and provides more results that can be generalized than those from clinical trials.

The third critical issue in the evaluation of the prognostic effect of comorbidity in patients with malignancy is the selection of the outcomes of interest. In fact, each comorbid condition may have different impacts on the outcome of the underlying malignancy, as well as on the eligibility of specific treatments and on their efficacy. In addition, outcomes such as the quality of life are turning out to be important endpoints.[9]

A further level of complexity is that comorbidity must be integrated in a more comprehensive geriatric assessment.[10] Comorbidities are not simply additive or synergistic in affecting the prognosis, but also strongly interact with other patient characteristics such as functional and nutritional status, cognition, psychological state and social support. Moreover, even in the absence of a clinically-evident disease, ageing may be associated with a progressive loss of the organ functional reserve needed to maintain physiological homeostasis under stress, resulting in a condition of frailty.

During the last decade, oncologists and geriatricians have begun to work together to integrate these principles into cancer care. Older patients with cancer are more likely to require functional assistance than those without cancer. In this clinical setting, a comprehensive geriatric assessment was demonstrated to predict survival as well as therapy-related toxicity and mortality.

Information on the role of comorbidity in cancer patients is mainly derived from studies on solid tumor populations, while their impact in hematologic malignancies is still largely unknown.

Myelodysplastic syndromes (MDS) are one of the most common hematologic malignancies in Western countries.[11] Its incidence in the general population is about 3.5-4 per 100,000 person-year. However, over the age of 70 years, incidence rises from 15 to 50 per 100,000 person-year.[12,13] Thus, it is very likely that comorbidity may emerge as a relevant clinical problem in patients with MDS.

In this issue of Haematologica/the hematology journal,[14] Zipperer and colleagues address the relevant issue of the prognostic impact of comorbidity on the natural history of MDS. The study by the Düsseldorf group documents for the first time the high prevalence of comorbidity in MDS patients and shows that comorbidity significantly worsens the prognosis of these subjects.

It is well-known that age has a significant effect on survival of the MDS population: the older the patient, the worse the prognosis.[15,16] The effect of demographic predictors is mainly noticeable in patients with low-risk MDS. In high-risk patients, age does not affect the natural history of the disease, while its effect may be relevant in limiting the eligibility for intensive treatments (Figure 1). The role of extra-hematologic comorbidity in determining these outcomes is to be clarified.

Causes of death in MDS patients may be related to the consequences of the progression of the disease into acute leukemia, or to clinical events outside leukemic evolution. The impact of comorbidity is as expected noticeable on non-leukemic death, which is mainly due to cardiac failure, infection, hemorrhage and hepatic cirrhosis (Figure 2).[15] In agreement with these data, cardiac disease and infections are reported by Zipperer and colleagues as the most common comorbidity in MDS patients.

The occurrence of non-leukemic death (NLD) is significantly different among the WHO categories, with a higher incidence in low-risk subgroups.[15,17] In these patients the cumulative probability of leukemic death tends to increase several years after the diagnosis, while the probability of non-leukemic death increases constantly from the time of diagnosis, and appears to competitively replace leukemic death as the major cause of death in these patients. Conversely, considering high-risk patients, the leukemic death rate rapidly increases to exceed the level of non-leukemic deaths (Figure 3).

Therefore, from a clinical point of view, problems related to the presence of comorbidity appear to be very different in low- and high-risk MDS. In low-risk patients they increase the risk of death, while in high-risk patients who mostly die from leukemic evolution, comorbidity seems to mainly influence eligibility for intensive treatment, treatment tolerance and post-therapeutic outcome.

In MDS there is a high prevalence of patients suffering from symptomatic anemia, and the onset of a regular transfusion requirement has been found to be associated with reduced survival.[11,15] Anemia has been recognized as a negative prognostic factor in the general population, as well as in many pathological conditions, in particular involving the cardiovascular system. Preliminary data suggested that in patients with MDS low hemoglobin levels are associated with increased cardiac remodeling and risk of NLD.[15] Therefore it may be hypothesized that cardiac comorbidity in MDS patients may have not just an additive detrimental effect *per se* but actively interacts with anemia in determining the clinical course

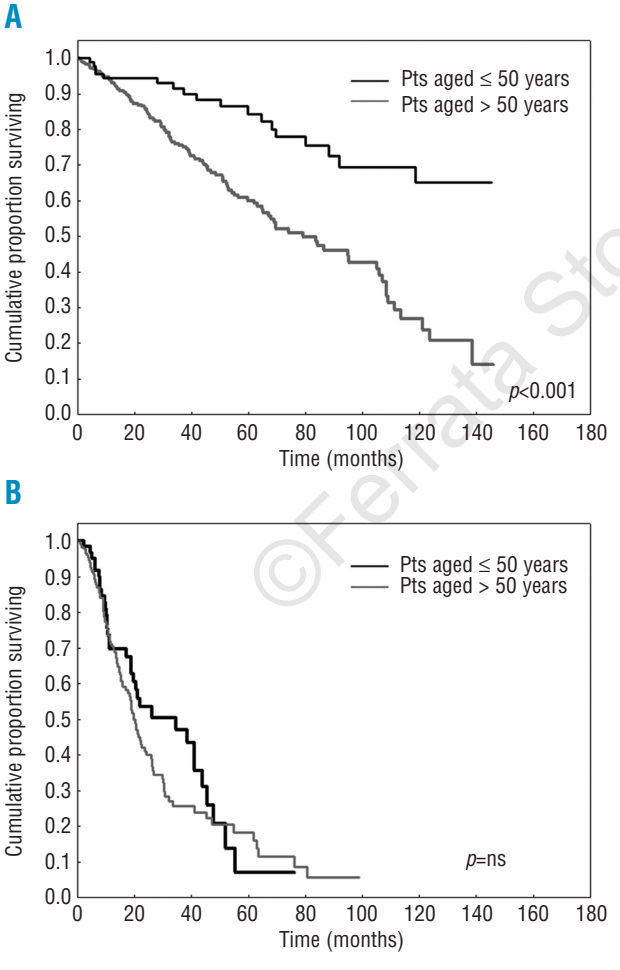

Figure 1. Cumulative probability of survival among 840 patients given a diagnosis of myelodysplastic syndrome at the Department of Hematology and Oncology, Policlinico San Matteo, Pavia Italy, 1992–2007 who are younger than 50 *vs.* >50 years of age. (A) Patients with refractory anemia or refractory cytopenia with multilineage dysplasia according to WHO criteria. (B) Patients with refractory anemia with excess blasts (types 1 and 2).

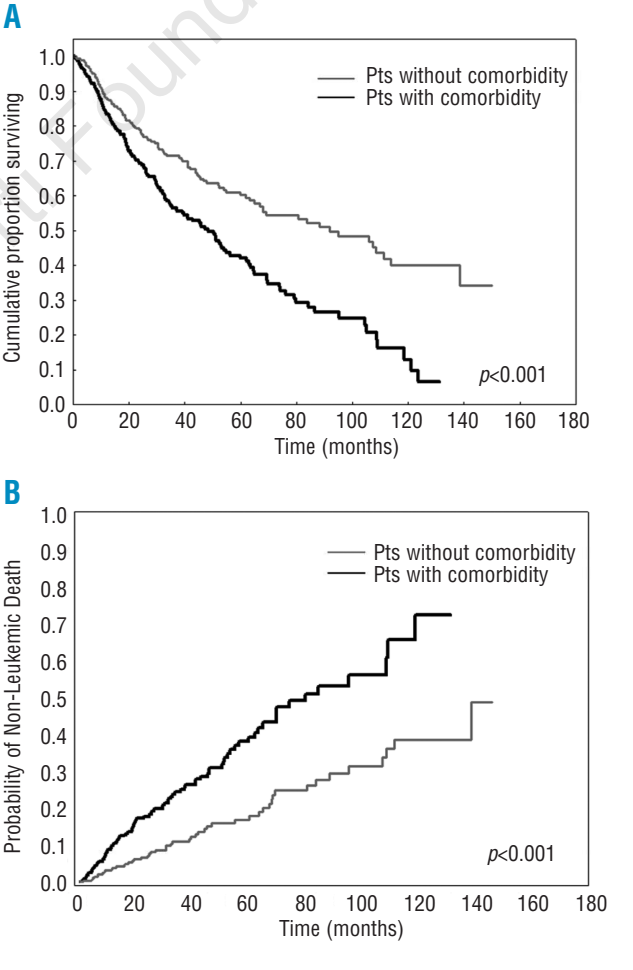

Figure 2. Cumulative probability of survival (A) and risk of non-leukemic death (B) among 840 patients given a diagnosis of myelodysplastic syndrome at the Department of Hematology and Oncology, Policlinico San Matteo, Pavia Italy, 1992–2007 according to the presence of extra-hematologic comorbidity at the time of diagnosis.

of the disease. In addition, the role of secondary iron overload in determining clinical organ dysfunction represents an interesting area of investigation. To date there is limited evidence on the role of iron in organ damage in patients with MDS. However, secondary iron overload as measured by serum ferritin was found to be associated with reduced survival in transfusion-dependent patients with MDS, with a more evident effect in patients with refractory anemia that have the longest median survival and are, therefore, more prone to developing the toxic effect of iron overload.[15]

The study by Zipperer and colleagues also addresses the relevant issue of the measurement of comorbidity in MDS. The application of a general comorbidity measure such as the CCI[7] to MDS patients failed to provide prognostic information. One possible reason is that most of the comorbid conditions included in the CCI are rarely observed in MDS patients. Moreover, common comorbidity like myocardial infarction or congestive heart failure, which are very relevant for anemic MDS patients, have a low weight in the CCI.

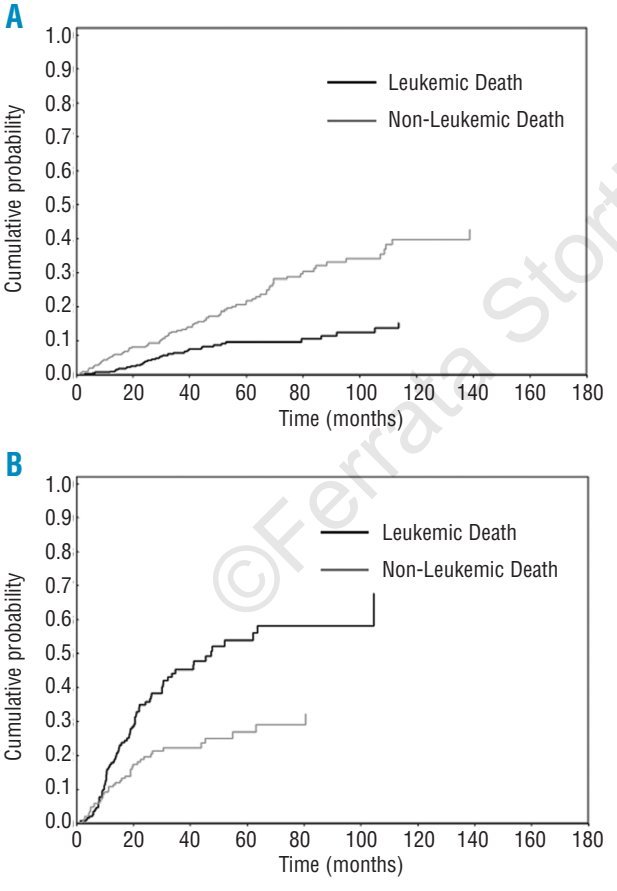

Figure 3. Cumulative probability of death attributed to disease complications/disease progression and to comorbidity by competing risk analysis among 840 patients given a diagnosis of myelodysplastic syndrome at the Department of Hematology and Oncology, Policlinico San Matteo, Pavia Italy, 1992–2007. (A) Patients with refractory anemia or refractory cytopenia with multilineage dysplasia according to WHO criteria; (B) Patients with refractory anemia with excess blasts (types 1 and 2). This analysis allows an estimate to be made of the cumulative incidence of a specified failure mode, compared to its competing risk over time.

Finally, the score does not account for the degree of severity of these conditions.

Recent findings showed that comorbidity assessment predicts post-transplantation outcome in MDS, and a hematopoietic cell transplantation (HCT)-specific comorbidity index (HCT-CI) was generated with the aim of improving sensitivity and specificity of CCI in this setting.[18] The most relevant modifications with respect to CCI were the inclusion of additional diseases clinically relevant for transplantation, and the introduction of objective laboratory and functional data in comorbidity definition. These modifications resulted in a significantly increased sensitivity in identifying patients with comorbid conditions compared to CCI, as well as in a more accurate prognostic stratification of these patients. HCT-CI was specifically validated in MDS patients receiving allogeneic transplantation.[19]

However, according to evidence-based guidelines[20] no more than 20% of MDS patients are eligible for intensive treatments with a curative aim (Malcovati L, unpublished data, 2005). Therefore, the results obtained in such a highly selected subset of patients cannot be easily applicable to the whole MDS population. Nevertheless, in the study of Zipperer and colleagues, HCT-CI allows a successful identification of a high proportion of MDS patients with relevant comorbidity. The score also provides prognostic information on untreated subjects with IPSS intermediate-2 and high-risk, but fails to stratify the outcome of low-risk patients. Overall, HCT-CI appears to be only partially adequate to study the clinical significance of comorbidity in MDS. Investigations aimed at defining MDS-specific comorbidity measures are warranted.

The improvement of clinical decision making in MDS demands a continuous effort to refine patient- and disease-specific prognostic factors. The accurate evaluation of extra-hematologic comorbidity must be part of the prognostic assessment of patients with MDS. This is expected to result in a more accurate selection of optimal candidates to intensive therapeutic procedures in high-risk disease. In addition, the prevention of non-hematologic complications is mandatory, especially in subjects with low-risk MDS, in order not to worsen their life expectancy or to preclude the eligibility of younger patients for intensive treatments.

Dr. Della Porta is a Reseacher in Clinical Oncology, and Dr. Malcovati a Researcher in Hematology at the University of Pavia Medical School, Pavia, Italy.

References

1. National Cancer Institute: Surveillance Epidemiology and End Results (SEER) registry. Bethesda, MD, National Cancer Institute. www.seer.cancer.gov.
2. Repetto L, Fratino L, Audisio RA, Venturino A, Gianni W, Vercelli M, et al. Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol 2002;20:494-502.
3. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. Jama 2004;291:2441-7.
4. Bouchardy C, Rapiti E, Fioretta G, Laissue P, Neyroud-

Caspar I, Schäfer P, et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol 2003;21:3580-7.
5. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061-7.
6. Geraci JM, Escalante CP, Freeman JL, Goodwin JS. Comorbid disease and cancer: the need for more relevant conceptual models in health services research. J Clin Oncol 2005;23:7399-404.
7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
8. Piccirillo JF, Spitznagel EL Jr, Vermani N, Costas I, Schnitzler M. Comparison of comorbidity indices for patients with head and neck cancer. Med Care 2004;42:482-6.
9. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008;358:1250-61.
10. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007;25: 1824-31.
11. Cazzola M, Malcovati L. Myelodysplastic syndromes--coping with ineffective hematopoiesis. N Engl J Med 2005;352: 536-58.
12. Germing U, Strupp C, Kündgen A, Bowen D, Aul C, Haas R, Gattermann N. No increase in age-specific incidence of myelodysplastic syndromes. Haematologica 2004;89:905-10.
13. Leone G, Pagano L, Ben-Yehuda D, Voso MT. Therapy-related leukemia and myelodysplasia: susceptibility and incidence. Haematologica 2007;92:1389-98.
14. Zipperer E, Pelz D, Nachtkamp K, Kuendgen A, Strupp C, Gattermann N, et al. The hematopoietic stem cell transplantation comorbidity index is of prognostic relevance for patients with myelodysplastic syndrome. Haematologica 2009;94:xxx-xxx.
15. Malcovati L, Della Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglino E, Passamonti F, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol 2005;23:7594-603.
16. Kuendgen A, Strupp C, Aivado M, Hildebrandt B, Haas R, Gattermann N, Germing U. Myelodysplastic syndromes in patients younger than age 50. J Clin Oncol 2006;24:5358-65.
17. Malcovati L, Della Porta MG, Cazzola M. Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. Haematologica 2006;91:1588-90.
18. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, Storer B. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005;106:2912-9.
19. Sorror ML, Sandmaier BM, Storer BE, Maris MB, Baron F, Maloney DG, et al. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. J Clin Oncol 2007;25: 4246-54.
20. Alessandrino EP, Amadori S, Barosi G, Cazzola M, Grossi A, Liberato LN, et al. Evidence- and consensus-based practice guidelines for the therapy of primary myelodysplastic syndromes. A statement from the Italian Society of Hematology. Haematologica 2002;87:1286-306.

The molecular basis of familial chronic lymphocytic leukemia

Dalemari Crowther-Swanepoel, and Richard S. Houlston
Section of Cancer Genetics, Institute of Cancer Research, Sutton, Surrey, UK. E-mail: richard.houlston@icr.ac.uk.
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It is now well established that inherited genetic predisposition plays an important part in defining individual susceptibility to most common solid tumors. Paradoxically, despite chronic lymphocytic leukemia (CLL) being the most common lymphoid malignancy in Western countries[1] and having a strong familial risk, our understanding of the genetic basis of CLL is only just starting to be recognized and its etiology elucidated.

Familial clustering of chronic lymphocytic leukemia

Over the last seven decades more than 100 families have been reported in the literature in which clustering of CLL has been documented. While not exclusively a consequence of genetic predisposition, familial aggregation provides strong evidence to support the role of inherited genetic factors in disease etiology. In a number of the families reported, CLL cosegregates with other B-cell lymphoproliferative disorders (LPD) such as Hodgkin's lymphoma (HL) suggesting that part of the familial predisposition could be mediated through pleiotropic mechanisms.[2-4] While most of the CLL pedigrees are nuclear families in which less than 4 family members have been affected, some spectacular multigenerational pedigrees have been described.[2,5] In addition to such families providing evidence for a strong familial basis to CLL the pattern of disease transmission in the pedigrees appears compatible with a model of inheritance where dominantly acting mutations confer a substantive risk of CLL.

Familial risks of chronic lymphocytic leukemia

Over the last 34 years, eight epidemiological case-control and cohort studies have systematically enumerated the risk of relatives of CLL patients developing CLL or other LPDs.[4, 6-10] Collectively these data provide evidence for a 2 to 8-fold elevated risk of CLL in case relatives.

In this issue of the journal, Goldin *et al.* have published the most comprehensive study of the risk of CLL and other LPDs in first-degree relatives of CLL cases to date.[11] This study was based on an analysis of 9,717 CLL cases and 38,159 controls ascertained through the Swedish Cancer Registry. Findings underscored CLL being characterized by a high familial relative risk (RR) – the RR of CLL in first-degree relatives of cases in this study was seen to be increased 8.5-fold. Furthermore, the risk of other non-Hodgkin's lymphoma was observed to be increased 1.9-fold. Evaluating NHL subtypes revealed a striking excess of indolent B-cell NHL, specifically lymphoplasmacytic lymphoma/Waldenström macroglobulinemia and hairy cell leukemia. These findings substantiate a relationship between the risk of CLL and other LPDs which has previously been anecdotally noted in case reports of single families and that may reflect the pleiotropic effects of an inherited predisposition.

The general incidence rates for CLL are nearly twice as high in men as in women. With familial CLL, however, the proportion of affected females is higher when