difference is clearly nonsignificant. For there to be evidence that the increased risk of being FLT3/ITD positive was negated by allogeneic transplantation, there would need to be interaction between the allografted patients and the autografted or chemotherapy-only patients. There is no such interaction for either relapse or overall survival. We did not present the test for interaction over the 3 groups in Figure 3, but the result for relapse is $\chi^2 = 1.8$ ($P = .4$) and for overall survival it is $\chi^2 = 9$ ($P = .6$). Hence, there is no evidence at all of heterogeneity, precluding the conclusion that allogeneic SCT modifies the risk of FLT3/ITD positivity. Similarly, Figure 4C of our paper does not show that “allograft recipients had the same relapse risk regardless of the FLT3/ITD status” because of the small number of events and wide confidence intervals. The assertion to the contrary by Meshinchi et al is a confusion of a lack of evidence of effect with evidence of lack of effect.2

To address the issue of whether allogeneic SCT modifies the poor prognosis associated with an FLT3/ITD, an “intention-to-treat” analysis in the form of a donor–versus–no donor comparison is preferable. This confirms the lower relapse rate associated with allogeneic SCT but indicates that this occurs in both the FLT3/ITD-positive and FLT3/ITD-negative patients. In their letter, Meshinchi et al construct a single table from our donor–versus–no donor analysis and the randomization to receive or not receive an autologous SC transplant. This is an injudicious comparison because patients with a donor are likely to have different characteristics from those entered into a randomization. The dangers of making such a comparison have been previously outlined.3 Furthermore, as we had pointed out in “Discussion,”1 the patients not receiving an autograft in the randomized comparison fared considerably worse than other patients in the trial who did not participate in the randomization and did not receive an autograft.

Meshinchi et al contend that “allograft may improve outcome in FLT3/ITD-positive AML,” and we agree with this, at least as far as relapse is concerned. We are not saying that FLT3/ITD-positive patients should not receive an allograft, rather that the presence of an FLT3/ITD should not be factored into the decision whether or not to perform allogeneic SCT, as the benefit of the allograft is also seen in the FLT3/ITD-negative patients. We are also not excluding the possibility that allogeneic SCT may be of greater benefit in the FLT3/ITD-positive patients, but the data do not yet support such a hypothesis. It is an important issue, which is why we advocate larger studies or a meta-analysis. In the interim, statistical “purity” should not be abandoned.

Rosemary E. Gale, Robert Hills, Keith Wheatley, Alan K. Burnett, and David C. Linch

Correspondence: Rosemary E. Gale, Department of Haematology, Royal Free and University College Medical School, 98 Ch trendy Mews, London WC1E 6 HX, United Kingdom; e-mail: rosemary.gale@ucl.ac.uk.

References


To the editor:

Chromosomal rearrangements involving the BCL3 locus are recurrent in classical Hodgkin and peripheral T-cell lymphoma

In a recent issue of Blood, Mathas et al1 suggested elevated BCL3 expression to be functionally important in classical Hodgkin lymphoma (cHL) and peripheral T-cell lymphoma (PTCL). The authors reported strong BCL3 protein expression in the vast majority of cHLs and a subset of PTCLs.1 These results corroborated similar immunohistochemical findings by Canoz et al.2

Mathas et al1 reported chromosomal gains of the BCL3 locus in chromosome band 19q13 as a potential cause of BCL3 upregulation in 3 of 6 cHL cell lines and 8 of 37 PTCLs. Here, we provide evidence that not only chromosomal gains but also translocations affecting the BCL3 locus are recurrent in cHL and PTCL.

A BCL3 break-apart fluorescence in situ hybridization (FISH) assay using differentially labeled bacterial artificial chromosome (BAC) clones was applied to a series of 20 cHLs, and BCL3 breakpoints were detected in 2 cases. In one cHL, in which cytogenetic analysis suggested a t(14;19),3 an IGH-BCL3 juxtaposition was proven by FISH (Figure 1A-B). This translocation is a recurrent event in B-cell chronic lymphatic leukemia4 (B-CLL), although there was no evidence for a concomitant or previous B-CLL in this case. As the immunoglobulin genes are downregulated in cHL,5 the pathogenetic significance of an IGH-BCL3 translocation remains uncertain. Unfortunately, no material was available for immunohistochemistry. In the second cHL, none of the IG loci were translocated to BCL3. Additionally, 3 (15%) of 20 cHLs showed gains of the BCL3 locus in the Hodgkin/Reed-Sternberg (HRS) cells exceeding the ploidy level (defined as median number of FISH signals for 12 different genomic loci; data not shown). Thus, the frequency of BCL3 gains in our series of primary cHLs was lower than that reported in cHL cell lines.1 However, our analyses did not consider the absolute number but the number of BCL3 copies relative to the ploidy level. Applying this approach to 4 cHL cell lines (HDLM-2, KM-H2, L428, and L1236), no gains of the BCL3 locus were detected, though the absolute numbers of signals were the same as those reported.1 These findings were corroborated by array–comparative genomic hybridization (CGH) analyses that failed to detect significant gains of BCL3 in these 4 cell lines (data not shown).

We additionally studied 3 PTCLs (2 unspecified and 1 angioimmunoblastic T-cell lymphoma) with a cytogenetically proven t(14;19)(q11;q13) with FISH break-apart probes for the TCRAD locus in 14q11 and BCL3 (Figure 1C-D). In all 3 cases, chromosomal breaks affecting both loci were detected. Colocalization of TCRAD and BCL3 was confirmed by 3-color assays, suggesting TCRAD-driven BCL3 activation as a possible novel oncogenic mechanism in T-cell neoplasms. Nuclear BCL3 protein expression was shown by immunohistochemistry in 2 PTCLs with available material (not shown). According to published cytogenetic data in

From www.bloodjournal.org by guest on September 7, 2017. For personal use only.
with the published immunohistochemical data on BCL3 expression\(^1,2\) and highlight the importance of this gene in B- and T-cell lymphomagenesis.

Jose I. Martin-Subero, Ivona Wlodarska, Christian Bastard, Jean-Michel Picquenot, Jorge Hoppener, Maciej Gieffing, Wolfram Klapper, and Reiner Siebert

Correspondence: Reiner Siebert, Institute of Human Genetics, University Hospital Schleswig-Holstein, Campus Kiel, Schwanenweg 24, 24105 Kiel, Germany; e-mail: r.siebert@medgen.uni-kiel.de.

The authors thank Claudia Becher and Dorit Schuster for their excellent technical assistance.

Supported by grants from the Deutsche Krebshilfe (70-3172-313/B1), the Fund for Scientific Research of Flanders (FWO-Vlaanderen, grant no. G.0338.01), and a Collaborative Experimental Scholarship for Central & Eastern Europe from the Federation of European Biochemical Societies (FEBS). M.G. receives a PhD fellowship from the President of the Polish Academy of Sciences.

J.M.-S. designed and performed research, analyzed data, and wrote the paper; I.W. and C.B. provided tumor samples and performed cytogenetic analyses; J.-M.P. provided tumor samples for immunohistochemistry; W.K. provided tumor samples, performed research, and was involved in histopathologic review; J.H. and M.G. performed research and analyzed data; and R.S. designed research, analyzed data, and wrote the paper.

References


Response:

Chromosomal rearrangements involving BCL3 support its pathogenetic role in classical Hodgkin and peripheral T-cell lymphoma

We recently described high expression of the putative proto-oncogene Bcl-3 in Hodgkin/Reed-Sternberg (HRS) cells of classical Hodgkin lymphoma (cHL) and a proportion of peripheral T-cell lymphomas (PTCLs), including anaplastic large-cell lymphomas (ALCLs).\(^1\) In cHL and ALCL cell lines, Bcl-3 contributes via induction of NF-kB–p50 homodimer activity to the constitutive NF-kB activity and might be involved in cell-cycle and apoptosis regulation. Bcl-3 was originally discovered by molecular characterization of the t(14;19)(q32.3;q13.2) translocation in B-cell chronic lymphocytic leukemia (B-CLL).\(^2\)

In this issue of Blood, Martin-Subero et al describe chromosomal rearrangements in cHL and PTCL that involve the BCL3 locus. These data provide interesting additional information concerning the possible underlying molecular mechanism of Bcl-3 upregulation in these lymphomas. Apart from a BCL3 fluorescence in situ hybridization (FISH) analysis for the detection of rearrangements involving the BCL3 locus, the authors investigated the number of BCL3 copies in HRS cells. Whereas we assessed in our analysis of HRS cell lines the absolute number of BCL3 copies per cell, Martin-Subero et al analyzed BCL3 copy number gains relative to the ploidy level. This analysis demonstrated that, in addition to BCL3 gains resulting from copy number gains of the entire chromosome (eg, in polyploid cells), intrachromosomal rearrangements of the BCL3 locus in HRS cells occur. In our opinion, all of these mechanisms could explain the finding of frequent Bcl-3 overexpression in cHL and PTCL. However, the results of Martin-Subero et al additionally point to a selection for chromosomal alterations involving the BCL3 locus that might lead to activation and overexpression of BCL3. These data further underline.
To the editor:

Thrombotic complications in patients with newly diagnosed multiple myeloma treated with lenalidomide and dexamethasone: benefit of aspirin prophylaxis

Lenalidomide (LEN) is an immunomodulatory compound with significant activity versus relapsed/refractory multiple myeloma (RRMM). In Blood, Rajkumar et al. reported striking efficacy of LEN plus dexamethasone (DEX) versus newly diagnosed multiple myeloma (NDMM). While structurally similar to thalidomide (THAL), also used to treat MM, LEN has a unique activity profile. Both agents appear to increase the risk of thromboembolic events (TEE), although the actual baseline incidence is unclear. The TEE incidence in NDMM patients receiving THAL+DEX without thrombosis prophylaxis is approximately 15%. An 8.5% incidence of TEE in RRMM patients getting DEX+LEN without routine prophylaxis has been reported. Rajkumar et al. described a 3% incidence in NDMM with DEX+LEN and daily aspirin (ASA; 80 mg or 325 mg).

The Southwest Oncology Group is conducting a double-blind randomized trial comparing DEX (40 mg/day on days 1-4, 9-11, and 17-20 every 35 days for 3 induction cycles, then 40 mg/day on days 1-4 and 15-18 every 28 days as maintenance thereafter) plus placebo versus DEX (same schedule) plus LEN (25 mg/day on days 1-28 every 35 days during induction, then 25 mg/day on days 1-21 every 28 days during maintenance). Crossover from DEX to DEX+LEN is permitted for progressive MM. Initially, no thrombosis prophylaxis was mandated. After 21 patients were enrolled, an increased incidence of TEEs in 1 arm became apparent: 9 (75%) of 12 patients receiving DEX+LEN developed TEEs (8 lower-extremity deep-vein thromboses with 2 pulmonary embolic events, 1 ischemic stroke) after a median of 50 days, versus 0 (0%) of 9 patients on DEX alone (P < .001). The study was modified to require 325 mg ASA daily, based on the low TEE incidence observed by Rajkumar et al., as well as a report showing low-dose ASA reduced TEE risk in MM patients receiving chemotherapy-thalidomide combinations.

As of October 31, 2005, 76 patients have been enrolled. Since mandating ASA prophylaxis, 6 TEEs have occurred among 55 additional patients: 4 (15%) of 26 randomized to DEX+LEN (P < .001 for comparison of TEE incidence on DEX+LEN before and after aspirin) and 2 (7%) of 29 on DEX alone (P = .41 for DEX vs DEX+LEN after ASA). Of interest, both of the patients randomized to DEX who developed clots had already crossed over from DEX to DEX+LEN due to progressive disease. One of these patients was noncompliant with ASA prophylaxis. Overall, 6 (19%) of 32 patients receiving DEX+LEN have developed TEEs since modification of the protocol to include ASA prophylaxis (P < .001 before vs after ASA).

In summary, although adding ASA markedly reduced the risk of TEEs in NDMM patients receiving DEX+LEN, we observed a much higher incidence of TEE than reported by Rajkumar et al. Potential reasons include higher DEX dose, longer LEN exposure during induction in our trial, or other factors such as possible differences in the use of recombinant erythropoietin. The 19% TEE incidence we observed is similar to that reported for NDMM patients treated with anthracycline-THAL combinations plus either 81 mg ASA or low-dose enoxaparin. At present, using one of these prophylaxis strategies during DEX+LEN treatment for NDMM is highly recommended. Further research is needed to determine the optimal prophylaxis strategy.

Jeffrey A. Zonder, Bart Barlogie, Brian G. M. Durie, Jason McCoy, John Crowley, and Mohammad A. Hussein

Correspondence: Jeffrey A. Zonder, Karmanos Cancer Institute, 4th Floor Hudson-Webber Cancer Research Center, 4100 John R, Detroit, MI 48201; e-mail: zonderj@karmanos.org.

Supported in part by Celgene Corporation.

References

Chromosomal rearrangements involving the \textit{BCL3} locus are recurrent in classical Hodgkin and peripheral T-cell lymphoma

Jose I. Martin-Subero, Iwona Wlodarska, Christian Bastard, Jean-Michel Picquenot, Jorge Höppner, Maciej Giefing, Wolfram Klapper and Reiner Siebert