Pseudo Pelger-Huët anomaly in myelodysplastic syndrome: hyposegmented or apoptotic neutrophil?

Huët first observed an abnormal hyposegmented neutrophil granulocyte in 1928, and a year later Pelger reported an additional case. Such a cell later became known as Pelger-Huët anomaly. In 1932 Huët pointed out its hereditary and systemic character. The Pelger-Huët anomaly is a familial anomaly that is transmitted as a Mendelian dominant trait but that is unaccompanied by any pathologic phenomenon. It is found in a heterozygous state in elderly populations characterized by peripheral cytopenias and dysplastic hematopoiesis. But dysplastic hematopoiesis is a feature not confined only to MDS: this feature is also seen during the evolution that might also facilitate homotypic myeloblast adhesion.

Anomalies resembling Pelger-Huët anomaly that are acquired rather than familial have been described as pseudo Pelger-Huët anomaly. The morphologic characteristic seen in pseudo Pelger-Huët anomaly is similar to Pelger-Huët anomaly. The acquired pseudo Pelger-Huët anomaly has been associated with pathologic features at disease presentation. A similar pattern is observed in AML, an observation that we report from our own data in the manuscript. But acquisition of the VEGF autocrine responsive phenotype may represent an early event in AML evolution that might also facilitate homotypic myeloblast adhesion.

Although we report the characteristic staining pattern for VEGF/receptor in isolated myelomonocytic precursors in 8 of 8 patients with refractory anemia, we do not describe ALIP in this low-risk FAB category, as stated by Dr Mangi. We fully agree with Dr Mangi that the International Prognostic Scoring System (IPSS) in MDS is a useful scoring system based upon clinical and pathologic features at disease presentation. Our series of patients was not restricted to bone marrow specimens obtained at diagnosis and includes patients with proliferative chronic myelomonocytic leukemia (CMML), which are excluded from the IPSS.

An important aspect of our study overlooked by Dr Mangi is that, while we and others have demonstrated the expression of VEGF in hematopoietic malignancies, this is one of the first reports to characterize the functional relevance as it relates to potential autocrine stimulation of tumor growth and survival. Such translational investigations are critical to the development of novel therapies targeting the VEGF-receptor axis and to thereby offer the potential to impact leukemia progenitor growth and development.

References

To the editor:

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From its first recognition until now, the presence of pseudo Pelger-Huët anomaly is considered to be the most specific dysplastic marker for the diagnosis of MDS without any bias. Recent studies have also included this morphologic abnormality as a prognostic marker in MDS. In the past our group has reported excessive intramedullary apoptosis of hematopoietic cells in MDS. Apoptosis was found to be pronounced in maturing/matured cells in the high-density fraction of the bone marrow (BM) aspirate and biopsy.

In light of the above findings in MDS and the current knowledge of morphology of apoptotic cells, we decided to evaluate whether the Pelger-Huët cells are apoptotic. BM aspirates and peripheral blood (PB) specimens from 56 MDS patients were examined for apoptosis using light microscopy (LM), electron microscopy (EM), and in situ end labeling (ISEL) of DNA, as described earlier. Of these, 25 patients had refractory anemia (RA), 12 were RA with ring sideroblasts (RARS), 13 were RA with excessive blasts (RAEB), 4 were RAEB in transfomration (RAEB-1, and 2 were chronic myelomonocytic leukemia (CMML). The patient population consisted of 34 males and 22 females, and the median age was 68 years (range, 26-85 years).

On examining the BM aspirate and PB of the MDS patients, 78% (44 of 56) of patients belonging to different FAB types showed the presence of characteristic Pelger-Huët anomaly by LM and EM (Figure 1). They were seen in both the PB and the BM aspirates of these patients. The median frequency of the pseudo Pelger-Huët cells was 3.8% (range, 1-34) in the PB and 4.6% (range, 2-38) in the BM aspirate. The incidence of these cells reported in this study was comparable to those reported earlier. Interestingly, both the high density (HD) and the low density (LD) fractions of the PB and BM aspirate compartments showed the presence of pseudo Pelger-Huët anomaly. In addition, a higher number of these cells were seen in the HD fraction than in the LD fraction (9.6% versus 4.2%; \( P = .0001 \)). Morphologically, 98% of these cells looked like mature granulocytes undergoing apoptosis. The electron microscopic morphology showed that both unilobed and bilobed cells were undergoing apoptosis. The cells showed characteristic apoptotic features in both the nucleus and the cytoplasm. The nucleus showed compact and segregated chromatin sharply delineated toward the periphery of the nucleus. Marked condensation of the cytoplasm with distorted organelles and mild convolution of the cellular outlines were noted. These findings were further confirmed by ISEL (Figure 1).

The above finding raises the question whether the pseudo Pelger-Huët cell is an anomaly or a manifestation of apoptosis. A normal neutrophil attains its matured multilobulated nuclear morphology subsequent to the mononuclear (pro/meta/myelocyte) and band-form stages. The mononuclear pseudo Pelger-Huët cells shown by different techniques in the figure thus may resemble an early myeloid cell undergoing apoptosis. Similarly, it is possible that the bilobulated pseudo Pelger-Huët cells may also be an apoptotic manifestation of the band cells or later stages prior to culminating in to multilobulated form. Pseudo Pelger-Huët cells thus may represent different stages of neutrophil differentiation undergoing apoptosis. The death of pseudo Pelger-Huët cells in the BM of MDS patients may be inflicted by the BM microenvironment that has been shown to have high amounts of proapoptotic cytokines such as tumor necrosis factor alpha (TNF-\( \alpha \)) and interferon gamma (IFN-\( \gamma \)).

References


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To the editor:

Alternate designs for conduct and analysis of phase I cancer trials

We have read with interest the paper by Press et al1 that reported a phase I/II trial of iodine-131-tositumomab in combination with etoposide, cyclophosphamide, and autologous stem cell transplantation for relapsing B-cell lymphomas.

Objectives, design, and analysis of the trial are very accurately reported, as well as the data (with the actual doses and toxicities of all 52 treated patients). The main objective of the trial was to estimate the maximum tolerated dose (MTD) of iodine-131-tositumomab, defined as the dose associated with a 25% toxic rate. Design and analysis of the trial were based on a grouped up-and-down scheme, using cohorts of 4 patients. The principal advantage of this method is its simplicity and its great ease of application. But we have some ethical and statistical concerns with the use of such a design in evaluating the MTD.

First, the observed toxic rate associated with the estimated MTD was 0.174 (4 of 23), as reported in Table 3. But such a statistical conclusion involves uncertainty. It should have been informative to give an estimate of the 95% confidence interval of the toxic rate associated with MTD, which can be exactly computed from the paper results at [0.05-0.388]. In addition, the estimated MTD was empirically defined by the dose received by 20 patients (ie, 5 cohorts), provided that the lower limit of the 80% one-sided confidence interval associated with the observed toxicity rate did not exceed the 25% target toxicity rate. This latter statistical restriction should be more clearly explained and justified.

Second, these up-and-down designs poorly address ethical concerns (such as minimal sample size) that have become a major issue in the conduct and analysis of dose-ranging phase I oncology trials. Several new approaches have been introduced that more explicitly address these concerns. They are usually derived from the continual reassessment method (CRM), a sequential Bayesian approach that allows, in defining the dose to be administered to the next patient (or the next cohort of patients), for incorporating evidence from previous experience and previous experiments jointly with information accumulated along the trial.2 Patients are entered sequentially, and the toxic probability associated with each dose level is updated, using Bayes formula together with the available information on doses and observed toxicities. Each patient of the next cohort is then treated at the dose level for which the updated toxicity rate is closest to the target (here, 25%). It facilitates a commonsense interpretation of statistical conclusions by allowing for direct probability statements, such as the probability that the toxic rate of a dose level is in some interval around the target. Moreover, this Bayesian (probability) interval for an unknown toxic rate can be regarded as having high probability of containing the unknown quantity, in contrast to a confidence interval, which may strictly be interpreted only in relation to a sequence of similar inferences that might be made in repeated practice. Additionally, Bayesian approach enables calculations of probabilities of future observations, from which several stopping rules can be derived, allowing an easy and reproducible decision either to continue patient accrual or to stop inclusions.3 We have retrospectively applied the CRM to the available data on the 47 patients who were actually administered the tositumomab. Using either 23 Gy (dose 2) or 25 Gy (dose 3) as the initial guess of MTD (as required by the Bayesian paradigm), we found from the updated dose-toxicity relationship that 25 Gy was the estimate of the MTD, with posterior toxic rate associated with MTD at 0.216 (95% Bayesian interval: [0.108-0.352], Figure 1A) or 0.188 ([0.089-0.316], Figure 1B), respectively. Our findings confirm the results of Press et al. Nevertheless, the sequential computation after each cohort of 4 patients of stopping rules based on the predictive distribution of the number of toxicities observed in the next 4 patients would have yielded to an earlier stopping of the accrual, at most after 36 patients.

We conclude that sequential Bayesian approaches may provide useful information on the dose-toxicity relationship so that its use in planning further phase I/II trials should be encouraged among investigators in hematology, as it has been done in other fields.4

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