Refractory anemia. This term has been obsolete for decades and should be made obsolete. It derives from an early effort to distinguish among nonhemolytic anemias by whether they did or did not respond to iron or specific vitamin-replacement therapy. Moreover, most of the “refractory anemias” are accompanied by varying degrees of abnormalities in the concentration or morphology of white cells and platelets, leading to fruitless efforts to subcategorize the varied disease phenotypes. A mutation in a multipotential hematopoietic cell can produce a nearly limitless variety of manifestations as the multitude of phenotypes (and genotypes) of acute myelogenous leukemia indicate. No two are quite the same in phenotypic features. This variety of form occurs even within disease subsets with apparent similar cytogenetic abnormalities. The move toward genetic classification will be useful to motivate molecularly targeted therapists, but the best classification of leukemia for the patient will be by the curative drug to which it responds (ie, cladribine-curable leukemia). Today, the anemias, bicytopenias, and multilineagepneas in the array of refractory anemias are known to be neoplasms, that is, the clonal expression of a mutant multipotential hematopoietic cell. Thus, the

To the editor:

Language and the clonal myeloid diseases

Medicine has been fraught with linguistic ambiguities. Some terms are anachronisms, some lack precision, and some are inconsistent with current knowledge of the pathobiology of human disease. This terminology is disruptive to communication and understanding. Although the handful of experts in a field may be able to put such diagnostic designations into perspective, patients, students, physicians, nurses, demographers, and epidemiologists studying these entities are often uncertain or confused as to their place in the spectrum of relevant diseases or in the approaches to their therapy. Such terms should be amended where possible, but such recategorizations require the imprimatur of some organization or group. Although the list is long, three noteworthy candidates for change are discussed below.

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References


Figure 1. Lamivudine nontreated, treated, and pretreated NHL patients. ALT values of HBV-infected NHL patients nontreated (○) (n = 3), treated with lamivudine after chemotherapy (□) (n = 9), and pretreated with lamivudine (during and after chemotherapy) (■) (n = 2).

Figure 2. ALT values of HBV-infected NHL patients nontreated (○) (n = 3), treated with lamivudine after chemotherapy (□) (n = 9), and pretreated with lamivudine (during and after chemotherapy) (■) (n = 2).
term “clonal anemia” or “clonal cytopenia” or an alternative, representative designation should be coined and used. In effect, these are more indolent forms of myelogenous leukemia, and the circumlocution institutionalized about 25 years ago needs to be rectified.

To add to this mismeasure, the misleading designation “refractory anemia with excess blasts” has extended the term “refractory anemia.” The overt appearance of marrow blast cells characteristic of myelogenous leukemia has been subjugated to anemia, breaking the time-honored principal that the designation of a neoplasm is based on the presence of the tumor cells not the extent of the neoplasm. We would consider it ludicrous to call cancer of the lung “bronchitis with excess bronchial cancer cells,” although bronchitis is present. Moreover, the phrase “excess blasts” is erroneous. This situation is not analogous to obesity, that is, excess fat cells. These are malignant cells, not too many normal myeloblasts. Even in the situation is not analogous to obesity, that is, excess fat cells. These are malignant cells, not too many normal myeloblasts. Even in the paper that lead to this terminology, the title used the phrase “refractory anemia with an excess of myeloblasts in the bone marrow (smoldering leukemia).” Thus the concept that 5 percent or lower of marrow blasts is likely to represent a remission after chemotherapy has been misapplied. At the time of disease presentation in an older child or adult, more than 1 percent myeloblasts in the presence of other lineage abnormalities is nearly always “myelogenous leukemia.” The rate of progression of a cancer based on the histologic or anatomic staging is irrelevant to the diagnosis.

For more elaborate arguments on the need to revisit this terminology, see Lichtman. The grouping of “refractory anemias” with “refractory anemia with excess blasts” neglects the fact that the former is often nonprogressive and survival is measured in years to decades. Although prone to clonal instability and evolution to overt myelogenous leukemia, they are more akin in morbidity and mortality to other chronic clonal disorders such as polycythemia vera or primary thrombocythemia, especially if controlled for age of onset. Indeed in modern terms, these manifestations of a mutated multipotential hematopoietic stem cell represent minimal or moderate deviation myelogenous leukemia that is not a neoplasm (clonal) of a multipotential hematopoietic cell, morbid, and capable of clonal instability, but they have less impact on life expectancy in populations affected than acute myelogenous leukemia. The overarching term for clonal anemias, clonal cytopenias, and oligoblastic myelogenous leukemia in current use, “myelodysplasia,” is a very unfortunate misnomer since dysplasia is a specific pathologic term qualitatively different from neoplasia (and from hypoplasia, hyperplasia, and metaplasia). These clonal disorders are myeloneoplasias with more vivid dysmorphia of cells on average than several other clonal myeloid disorders. But they are often not more dysmorphic than blood cells in agnogenic myeloid metaplasia, which is excluded from the category of myelodysplasia, yet it fits every criterion. Idiopathic fibrosis or agnogenic myeloid metaplasia was initially described in 1879 as a myelogenous leukemia, which it is. Again, our predecessors have been distracted by epiphenomena, understandable perhaps in the context of the knowledge base of the time. To consider a patient with tricytopenia, qualitative (dysmorphic and functional) abnormalities of red cells, neutrophils and platelets, and 8 percent blast cells in the marrow to have a dysplasia or refractory anemia is nonsensical. Students, medical journalists, physicians, epidemiologists, and demographers are befuddled by myelodysplasia. This confusion is fostered by the principal textbooks of medicine grouping myelodysplasia (a myelogenous neoplasm) with aplastic anemia (usually an autoimmune disease), a horrendous distortion of pathobiology. It is time for the American Society of Hematology or a like organization to provide the leadership required to propose an appropriate nosology for the myelogenous leukemias. The recent World Health Organization effort has fallen short because of a timid approach to change. For further rationale for the need to rectify this erroneous term and for thoughts on classification, see Lichtman.

Differentiation therapy. The term “differentiation” has been misapplied to studies of myeloid leukemia treatment. Thus the terms differentiating agents and differentiation therapy have been used to describe maturation of cells already differentiated to monopotent progenitors. These cells are capable of maturation but not differentiation, and the agents that facilitate maturation are not differentiating agents. Moreover, the maturation of human leukemic promyelocytes results in pathologic phenocopies of neutrophils. In many respects, acute myelogenous leukemia is as much a disorder of maturation as of differentiation, although all aspects of hematopoietic multipotential or oligopotential progenitor cell function may be pathologic. Thus progenitors of the various blood cell lineages have “differentiated,” but their behavior as oligopotential progenitors is profoundly disordered. For a more comprehensive argument for the distinction between maturation and differentiation, see Lichtman.

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References


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