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To the editor:

Expression of the hemoglobin scavenger receptor (CD163/HbSR) as immunophenotypic marker of monocytic lineage in acute myeloid leukemia

The hemoglobin-haptoglobin scavenger receptor (CD163/HbSR) is a monocyte/macrophage-restricted transmembrane protein of the scavenger receptor cysteine-rich family.[1] Antigen expression is related to monocyte/macrophage differentiation, with weak expression on peripheral blood monocytes and abundant expression on the majority of tissue macrophages.[2-4] To clarify[2,3,5] whether CD163/HbSR is also expressed on leukemic cells committed to the monocytic lineage, we measured cell-surface expression of CD163/HbSR on leukemic blast cells of 78 patients with acute myeloid leukemia (AML).

AML diagnosis was established by morphology and cytochemistry according to French-American-British (FAB) criteria and immunophenotyping.[6] Cases were subclassified as M0 (n = 2), M1 (n = 9), M2, (n = 26), M3 (n = 5), M4 (n = 12), M5 (n = 19), M6 (n = 4), and M7 (n = 1). Density gradient–separated peripheral blood mononuclear cells were stained with fluorescein isothiocyanate (FITC)–labeled anti-CD163 antibody (clone 5C6-FAT; BMA Biomedicals, Augst, Switzerland) or an isotype control antibody (BD Biosciences, Heidelberg, Germany) for measurement of cell-surface CD163/HbSR expression by flow cytometry. Of 47 patients with AML subtypes other than M4 or M5, 41 (87%) had no or only minimal expression of CD163/HbSR (Figure 1). In the remaining 6 patients, 5% to 8% of the leukemic blasts stained positively for the antigen when compared with the isotype control antibody. In none of the patients, however, did antigen expression exceed 8%. By comparison, 3 of 12 patients with AML M4 and 16 of 19 patients with AML M5 had CD163/HbSR expression 10% or higher (Figure 1). At the time of initial diagnosis, 2 patients with AML M5 were treated with glucocorticoids, drugs that are known to increase CD163/HbSR expression on normal macrophages;[7] their effect on antigen expression on malignant cells is, however, unknown.

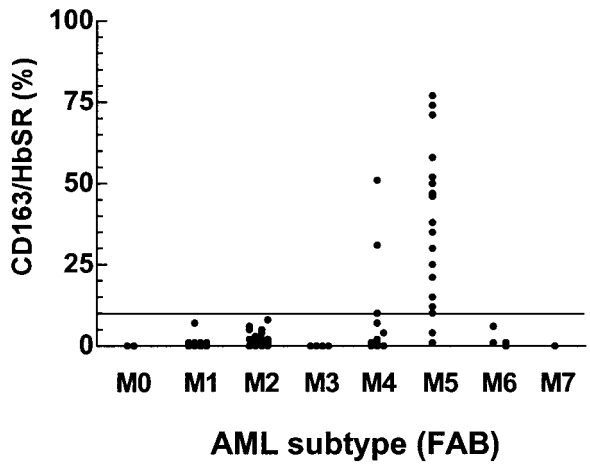

Figure 1. CD163/HbSR expression on mononuclear cells from patients with AML. Surface expression of CD163/HbSR on blast cells of patients with AML subtypes M0 to M7. None of the patients with AML other than M4 or M5 had CD163 expression higher than 8%. In contrast, 3 of 12 patients with M4 and 16 of 19 patients with M5 had CD163/HbSR expression 10% or higher.

In line with this lineage-restricted antigen expression, we observed strong correlations between CD163/HbSR and other markers predominantly found in monocytic leukemia,[8,9] such as CD14, CD64, and lysozyme (Table 1). Weaker correlations were found between CD163/HbSR and the myeloid markers CD15, CD33, CDw65, the percentage of unspecific esterase-positive blast cells, and transcobalamin II[10] (Table 1), but not for CD13 and CD117 (not shown). In addition, weak inverse correlations were found between CD163/HbSR expression and positivity of cytochemical staining for peroxidase and chloroacetate esterase and flow cytometric detection of intracellular myeloperoxidase (not shown), markers which are usually not expressed by monocytic leukemias.[6] A weak correlation was also found for CD163/HbSR and blood levels of C-reactive protein, possibly reflecting the acute-phase regulated expression of CD163/HbSR.

In conclusion, these results confirm early studies[2,3] and demonstrate that CD163/HbSR is expressed not only on mature monocytes and macrophages but also on leukemic cells. We found the antigen exclusively on the majority of monocytic and a significant subset of myelomonocytic leukemias, suggesting that the restriction of CD163/HbSR expression to cells committed to the monocytic lineage is preserved beyond malignant transformation; this

Table 1. Correlation of CD163/HbSR expression with expression of other differentiation antigens, cytochemical stains, and plasma parameters

Parameter	*p* (95% CI)	*P*	n
CD14	0.7495 (0.6283-0.8351)	<.0001	78
CD15	0.2758 (0.0500-0.4747)	<.015	78
CD33	0.3064 (0.0801-0.5026)	<.008	76
CD64	0.7265 (0.5948-0.8202)	<.0001	76
CDw65	0.4369 (0.2249-0.6094)	<.0001	74
Unspecific esterase	0.3140 (0.0745-0.5193)	<.01	68
Lysozyme	0.6444 (0.4811-0.7645)	<.0001	73
C-reactive protein	0.2815 (0.0514-0.4833)	<.015	75
Transcobalamin II	0.3015 (0.0715-0.5011)	<.01	74

Results from Spearman rank correlations are shown. CI denotes confidence interval.

lineage-restricted pattern of antigen expression may thus be useful for the immunophenotypic subclassification of leukemias.

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To the editor:

Is iron gluconate really safer than iron dextran?

Parenteral supplementation of iron is required in some patients with iron deficiency, including those with oral iron intolerance, chronic uncorrected bleeding, malabsorption, gastrointestinal inflammatory disease, dialysis dependence, or failure to take prescribed oral iron. A more rapid increase in hemoglobin production occurs after intravenous administration, which may be valuable in anemic patients and chronic bleeding patients. Unlike oral iron, the full dose of intravenous iron is delivered to the bone marrow and saturates tissue stores.[1,2]

The 2 popular forms of available parenteral iron in the United States are iron dextran and iron gluconate. Despite their value, intravenous iron therapy carries the potential for serious allergic reactions. In 1980, Hamstra et al examined over 2000 infusions of iron dextran among 481 patients and reported that 26% of patients experienced side effects, of which the majority were mild and self-limited. Of the reactions, 2% were considered "severe" allergic and 0.6% were classified as anaphylactoid. Most reactions were reported to occur immediately during the infusion of a test dose. As a result, administration of a test dose is now recommended to monitor patients for reactions.[1]

In contrast, iron gluconate is considered to have a lower reaction rate and a test dose is not recommended by the manufacturer. During the years of 1992 to 1996, Faich and Strobos reported 3.3 allergic events per million doses per year with iron gluconate and 8.7 allergic events per million doses per year with iron dextran.[3] No fatalities were associated with iron gluconate between 1976 to 1996. However, 31 fatalities among 196 allergy/anaphylactic cases were recorded between 1976 to 1996 for iron dextran, translating into a case fatality rate of 15.8% for iron dextran.[3] Other studies have reported similar high rates of allergic reactions for iron dextran.[4-6] As a result, several authors have advocated the use of iron gluconate over iron dextran, in order to avoid serious reactions. For example, The University of Iowa Health Care Center uses only iron gluconate despite the need for multiple dosing.[7]

Table 1. Reactions to iron dextran versus iron gluconate

	Iron dextran* (%)	Iron gluconate† (%)
Severe reaction	1 (2.6)	0 (0)
Moderate reaction	3 (7.7)	1 (3.8)
Mild reaction	4 (10.3)	5 (19.2)
No reaction	22	20
Total no. reactions	8 = 20.5% of infusions	6 = 23% of infusions

*Total 39 infusions; 32 patients.
†Total 26 infusions; 4 patients.

We report here a chart review of recorded reactions over the past 3 years (1999-2002) to intravenous infusions of iron dextran and iron gluconate administered in the outpatient Blood Transfusion Center at Massachusetts General Hospital, Boston. A total of 65 infusions of either iron dextran (INFeD, Schein) or iron gluconate (Ferrlecit, Schein, Morristown, NJ) were performed among 35 patients over the 3-year period. All patients were directly observed for allergic reactions and reactions were recorded.

We grouped the resulting reactions into 3 categories: severe (reactions such as anaphylactoid, shock, and cardiovascular collapse); moderate (reactions such as dyspnea, severe urticaria, and neck and back spasm in which the infusion was stopped and patient did not tolerate further infusion); and mild (reactions such as headache, dizziness, tachycardia, and hypertension in which the infusion was stopped but the patient subsequently completed the infusion). Over the 3-year period, an average of 21.5% (14/65) of infusions demonstrated some form of mild, moderate, or severe reaction. Of these reactions, only 1 reaction was severe, 4 were moderate, and the remainder were mild. As shown in Table 1, the rate of acute allergic reactions was comparable with the 2 preparations.

As previously reported by others, our data suggest a high rate of acute reactions to intravenous iron. When compared with other commonly prescribed medications, intravenous iron has an extremely high rate of adverse events. In contrast to previous reports, we have found that acute allergic reactions appear to be as common with iron gluconate as with iron dextran. Our findings are not explained by a selection bias (use of iron gluconate in patients with prior reactions to iron dextran) because only one patient who reacted to iron gluconate had had a prior reaction to iron dextran.[7] Our results challenge the notion that iron gluconate, which requires 8 infusions in place of the single infusion of iron dextran, is a safer