by LIBS6 and fibrinogen, without affecting primary aggregation, although full irreversible aggregation was impaired. But inhibition of full, irreversible aggregation by wortmannin did not impair thromboxane A2 accumulation in response to LIBS6 plus fibrinogen. These data suggest that the close platelet-to-platelet contact that is brought about by platelet aggregation (primary or full) is not sufficient to generate thromboxane A2 and depends on signaling from the ADP receptors. Hence we disagree with the interpretation of Cattaneo et al of the previously published results from several laboratories. We stand by our interpretation of our results that outside-in signaling from both the integrin αIIβ3 and the P2 receptors is required for ADP-induced thromboxane A2 generation in platelets. We agree with Cattaneo et al that ADP-induced thromboxane generation is greatly enhanced and can be seen in most healthy individuals when extracellular calcium is decreased to micromolar levels.

To the editor:

Myelodysplastic syndromes: prognostic significance of multilineage dysplasia in patients with refractory anemia or refractory anemia with ringed sideroblasts

We read with interest the recent paper by Nosslinger et al1 comparing the French-American-British (FAB) and the World Health Organization (WHO) classifications on 431 unselected patients with myelodysplastic syndromes (MDS). We were particularly interested in their analysis of patients (n = 91) with refractory cytopenia with multilineage dysplasia (RC + Dys), which showed no significant difference in the median survival when compared to those (n = 47) with refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS). We wish to report our experience (in a tertiary referral center) in patients with RA or RARS, classified according to the extent of dysplasia (ie, single- vs multilineage dysplasia).

We have studied 88 consecutive MDS patients with RA or RARS between January 1992 and January 1999. Clinical details and survival data were reviewed; bone marrow aspiration slides were examined and classified according to the WHO criteria for lineage dysplasia. Twenty-four patients were excluded from the study because of insufficient clinical information on survival (n = 20), death occurring within 4 weeks of diagnosis (n = 3), or treatment with bone marrow transplantation (n = 1).

The median age of patients with RA/RARS and single-lineage dysplasia was 74.7 years; median age of patients with bi- or trilineage dysplasia was 76 years. All but one patient (who had dysthrombopoiesis) in the single dysplasia groups had erythroid dysplasia.

In the RA group, patients with single-lineage dysplasia had a median survival of 32.8 months (range, 3-96 months) compared to 14.2 months (range, 3-53 months) in patients with multilineage dysplasia; the difference was significant (P < .05). Similarly, differences in survival were evident in the RARS groups with a median survival of 40.6 months (range, 2-85 months) in those with single-lineage dysplasia compared to 18.8 months (range, 3-69 months) in those with multilineage dysplasia. These results did not reach statistical significance. However, when we combined RA and RARS patients, we observed highly significant differences in survival times between those with single-lineage dysplasia (median survival [MS] 36.3 months) and those with multilineage dysplasia (MS 14.9 months). At the time of analysis, 59% (20/34) of patients with single-lineage dysplasia were alive, but only 10% (3/30) of patients with multilineage dysplasia were alive.

Cytogenetic studies showed abnormalities in 26% of all patients, but only 16% (8 patients) had results that conferred a worse prognosis ("intermediate risk" = 3, "poor risk" = 5).2 The majority of patients with adverse-risk cytogenetics had multilineage dysplasia (7/8). There was, as expected, a major difference in median survival between the 2 groups (30.5 months vs 7.9 months).

We did not find cytopenias predictive of the presence of multilineage dysplasia, nor did we find a difference in survival between those with 2 or 3 cytopenias (24.8 months) and those without (26.2 months).

The International Prognostic Scoring System (IPSS) stratification3 of the 64 patients were as follows: “low-risk” = 26; “intermediate 1 (INT-1) risk” = 20; and “INT-2 risk” = 3. The IPSS could not be applied to 15 patients because of a lack of cytogenetics.

Table 1 shows the relationship of median survival to various prognostic scoring systems in combined RA and RARS groups. Overall, combining the IPSS with lineage dysplasia had greater prognostic power than IPSS alone in these so-called good-risk FAB subtypes. Our findings are similar to those reported by Rosati et al4

| Table 1. Relationship of median survival to various scoring systems in combined RA and RARS group |
|-----------------------------------------------|-----------------|-------------|------------------------|
| Scoring system | Prognostic level | Median survival (months) | Statistical significance (P) |
| Lineage dysplasia | Single | 36.3 | < .01 |
| | Multiple | 14.9 | |
| IPSS | Low | 39.1 | > .05 |
| | INT-1 | 25.2 | |
| | INT-2 | 8.3 | |
| IPSS and dysplasia | Low + single | 42.5 | < .05 |
| | Low + multiple | 11.1 | |
| | INT-1 + single | 29.6 | |
| | INT-1 + multiple | 10.1 | |

References


and Matsuda et al,\textsuperscript{5} supporting the WHO classification of MDS and justifying the identification of patients with multilineage dysplasia in the RC + Dys subgroup.

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References


Response:

Controversy in MDS classification

We read with interest the letter to the editor entitled “Myelodysplastic syndromes: prognostic significance of multilineage dysplasia in patients with refractory anemia or refractory anemia with ringed sideroblasts” by Dunkley et al presenting their data from myelodysplastic syndrome (MDS) patients with less than 5% medullary blasts classified according to the World Health Organization (WHO) classification.\textsuperscript{1}

Although some published data provides evidence that presence of dysplastic features in 2 or 3 cell lineages has a negative impact on the survival duration of MDS patients with less than 5% medullary blasts at the time of diagnosis,\textsuperscript{2-4} our own data from 189 MDS patients without excess of blasts cannot support this hypothesis.\textsuperscript{5} As published data are inconsistent, Dunkley et al’s letter addresses an important problem concerning definition, classification, and prognosis of early stage myelodysplastic syndromes.

The study population of 64 patients presented by the authors is quite small. As this cohort is divided into 4 subgroups (15-20 patients in each subgroup; the exact number is not mentioned in the text), the explanatory strength of the (significant) results of Dunkley et al is not entirely convincing. It remains to be investigated whether the prognostic value persists when the comparison is controlled for other aspects (eg, the IPSS). Also the generalizability of the results is unclear.

Furthermore, the median survival times of the 2 small subgroups RA and RARS with single-lineage dysplasia of 32.8 and 40.6 months, respectively, are quite short compared to the majority of published data.\textsuperscript{4,7} The median survival durations of these MDS entities are usually around 55 to 60 months, even if the patients are classified according to the French-American-British (FAB) criteria. Similarly, the median survival durations of the small subgroups RA and RARS with multilineage dysplasia of 14.2 and 18.8 months, respectively, are short. It should be noted that these patients still present with less than 5% blast cells in the bone marrow at the time of diagnosis.

We agree as pointed out by the authors adverse-risk cytogenetics (according to the IPSS) in MDS patients correlate with bad prognosis and shorter survival.\textsuperscript{6-9} Moreover, the authors discuss that multilineage dysplastic features correlate with severe cytogenetic abnormalities. To our knowledge, no paper has been published supporting this hypothesis in MDS. Nevertheless, this is an important issue that cannot be adequately addressed by this letter because of the small patient cohort.

As recently discussed at the last American Society of Hematology meeting, the exact definition of dysplasia, especially the percentage of dysplastic cells in each lineage, seems to be of importance. We would therefore be interested in the threshold fixed by Dunkley et al for definition of presence of dysplasia in the 3 different cell lineages.

In conclusion the authors raise important questions concerning classification, prognosis, and consequently treatment requirement in patients with early stage MDS. These cannot be answered because of the low patient number in this study. Because of the heterogeneous nature of MDS, larger studies are warranted in order to reach answers to these questions.

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Myelodysplastic syndromes: prognostic significance of multilineage dysplasia in patients with refractory anemia or refractory anemia with ringed sideroblasts

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