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Cognitive side effects of myeloablative allogeneic hematopoietic cell transplantation

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Cancer patients and the providers who care for them are becoming increasingly concerned that cancer treatments may cause long-term cognitive changes that can negatively impact attainment of educational and work goals and general quality of life. A growing body of literature has suggested that long-term changes in cognitive functioning can be associated with a variety of systemic cancer treatments, including high-dose chemotherapy and stem cell transplantation, standard dose chemotherapy, and biologic response modifiers. However, a major problem with this literature is that few longitudinal studies that include pretreatment assessments and long-term follow-up of cognitive functioning have been reported. In the current issue, Syrjala and colleagues report the first large-scale, neuropsychological study that assessed patients undergoing myeloablative allogeneic hematopoietic cell transplantation (HCT) prior to treatment and at 80 days and 1 year after transplantation.

The results of the study demonstrated a significant reduction in performance on all tests of cognitive functioning at the 80-day posttransplantation assessment; however, performance returned to pretreatment levels at the 1-year assessment on all measures except for grip strength and motor dexterity. Interestingly, a higher percentage of patients than expected scored below published norms prior to transplantation, and performance on tests of verbal fluency and memory were below norms at all 3 testing points. This pattern of results illustrates the critical importance of longitudinal studies. Previous studies that have assessed patients only after treatment have interpreted similar percentages of below normative performance as an indication of the impact of the cancer treatment under study; whereas Syrjala et al were able to demonstrate that similar levels of impairment were, in fact, present before treatment.

Improvement in methodology does not necessarily eliminate all ambiguity from the interpretation of the results, as the authors recognize. From a patient’s point of view, the most positive interpretation would be that HCT causes short-term cognitive changes but not long-term cognitive deficits. However, as the authors discuss, the pretreatment performance on the neuropsychological tests may have been lowered due to psychological distress, medical illness, or medications that could have had sedating or other effects on the central nervous system, and may not have represented a “true” measure of cognitive capabilities. In this scenario, one might have predicted that to conclude that HCT had no adverse effects on cognitive functioning would require 1-year test scores above pretreatment levels. An alternative hypothesis is that only a subgroup, perhaps the minority, of patients is vulnerable to long-term cognitive problems secondary to cancer treatments. Therefore, examining groups of patients may mask a pattern of results suggesting that most patients recover to normal levels of cognitive functioning after treatment, whereas a subgroup of patients continues to experience deficits. Data from their study provide some support for this hypothesis: patients who had not received chemotherapy, other than hydroxyurea, prior to HCT and patients not receiving chronic graft-versus-host disease medications at 1 year were at lower risk for cognitive impairment at the 1-year assessment. Genetic, hormonal, and immunologic factors may also be important in determining vulnerability to cognitive changes associated with cancer treatments. The study reported by Syrjala and colleagues represents a significant advancement in understanding cognitive changes associated with HCT and is a model for future research in this area.

REFERENCES

Comment on Kanaji et al, page 3161

A tail with a leading role in megakaryocytes: the glycoprotein Ib

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Megakaryocytes possess a unique internal programming that allows an evolving response to a cytokine, thrombopoietin (TPO), including cellular expansion followed by polyploidization and maturation. The study of this lineage has been greatly aided by analysis of genetically modified mice and/or models of related human syndromes.

The Bernard-Soulier syndrome is associated with abnormal bone marrow megakaryocytes with poorly developed demarcation membranes, giant circulating platelets, and a reduced platelet count (coined as macrothrombocytopenia). The genetic basis of this syndrome has long been recognized as caused by mutations that impair expression of a multisubunit receptor, the glycoprotein (GP) Ib-IX complex. The mouse phenotype mimicking the human Bernard-Soulier syndrome can be salvaged by expression of a human GP Ibα transgene. In this issue of Blood, Kanaji and colleagues describe a series of elegant experiments that explore the importance of the cytoplasmic tail of GP Ib in rescuing mice from the Bernard-Soulier–like phenotypes. Using the megakaryocyte-specific platelet factor 4 promoter, these investigators generated a transgenic mouse line expressing onto a GP Ibα knock-out background a variant human GP Ibα subunit lacking the 6 terminal residues 605–610 on the cytoplasmic tail. This system was compared with the rescue of the GP Ibα null phenotype produced by a wild-type human GP Ibα allele. The cytoplasmic tail was chosen as a target mainly because it has been previously shown to be critical for binding to the signal transduction protein 14-3-3ε. The latter has been implicated in various processes that have been described by others to affect megakaryocyte proliferation and/or ploidy (eg, Drachman et al). 14-3-3ε influences intracellular signaling pathways (eg, Raf, MLK, MEKK, phosphatidylinositol-3 [PI3] kinase, IRS–1), cell cycling (eg, Cdc25, Wee1, CDK2, centrosome), apoptosis (eg, BAD, ASK–1), and the regulation of transcription (eg, FKHL1, DAF–16, p53, TAZ, TLX–2, histone deacetylase).

The phenotypes in the new transgenic models generated by Kanaji et al illustrate an involvement of the GP Ibα cytoplasmic tail in thrombopoietin-mediated events, including megakaryocyte proliferation, polyploidization, and the expression of apoptotic markers in maturing megakaryocytes. Furthermore, this study demonstrates an increase in thrombopoietin–mediated Akt phosphorylation in the truncated variant, leading the authors to hypothesize that a GP Ibα/14-3-3ε/PI3-kinase complex is involved in regulating thrombopoietin–mediated responses (see figure).

A hypothesis is presented whereby the cytoplasmic tail of GP Ibα sequesters signaling proteins, such as 14-3-3ε and PI3K, and down-regulates the Akt-dependent pathway. The authors speculate that in the truncated GP Ibα variant, a shift in the PI3K/Akt axis results in increased Akt activation and downstream consequences of increased endomitosis and accumulation of a greater percentage of high ploidy megakaryocytes. Although this is an appealing contention, it awaits further analyses to demonstrate a GP Ibα/14-3-3ε/PI3-kinase complex in vivo. It will also be of great interest to examine whether excess (via overexpression) of full-length versus a cytoplasmic tail portion of GP Ib results in greater sequestration of this complex and hindrance of thrombopoietin–related signaling.

Finally, while this study demonstrates that the molecular basis of the macrothrombocytopenia is linked to an absence of the cytoplasmic tail of the GP Ibα subunit of the GP Ibα-IX complex, the authors rightfully point out that a role for the extracytoplasmic domains of the complex cannot be excluded.

GP Ibα expression, megakaryocyte proliferation, and differentiation. See the complete figure in the article beginning on page 3161.
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