that myo-inositol can be much more heavily phosphorylated in cells, including versions of inositol in which all six \(-\)OH groups contain phosphate (inositol hexakisphosphate, or IP\(_6\), as depicted in the figure), or even more highly phosphorylated forms, termed inositol pyrophosphates (reviewed by Wilson et al\(^8\)). In these latter molecules, at least one of the \(-\)OH groups contains monophosphate (yielding IP\(_7\) or IP\(_8\), with 7 or 8 attached phosphates, respectively). Many of the enzymes responsible for synthesizing inositol pyrophosphates use IP\(_6\) (see figure) as the substrate, including, in mammals, 3 isozymes of the enzyme, inositol hexakisphosphate kinase (IP\(_6\)K). The IP\(_6\)K1 isozyme has been knocked out in mice, resulting in lower body weight, reduced insulin levels/insulin hypersensitivity, and defective spermatogenesis.\(^9\)

Ghosh et al\(^1\) cleverly noted that yeast lacking the enzyme equivalent to IP\(_6\)K are not only depleted of inositol pyrophosphates but that they also, perhaps surprisingly, have severely reduced levels of polyphosphate.\(^10\) Reasoning that a metabolic link between inositol pyrophosphates and polyphosphate may also exist in mammals, they explored the use of IP\(_6\)K1 knockout mice as a means of generating animals with lower levels of polyphosphate in their platelets. In the present study,\(^1\) they now report that, while the platelets of homozygous IP\(_6\)K1 knockout mice have normal-appearing dense granules, these platelets have a roughly 3-fold reduction in polyphosphate levels. Furthermore, in in vitro studies, they report that the platelets from these animals exhibited slower platelet aggregation, supported lengthened clotting times when platelet releasates were added to plasma, and exhibited lower incorporation of polyphosphate into fibrin clots (with concomitantly altered clot ultrastructure that could be rescued by exogenous polyphosphate), compared with studies performed using platelets from wild-type littermates. In vivo, they demonstrated longer tail bleeding times and greater resistance to thromboembolism in the homozygous IP\(_6\)K1 knockout mice compared with wild-type littermates. Because inositol pyrophosphates play roles in energy metabolism in yeast, Ghosh et al took pains to demonstrate that the levels of adenosine 5\(^{-}\)diphosphate (ADP) and adenosine triphosphate (ATP) in platelets from their knockout mice were normal, so the reduced platelet-mediated functions in these animals were not simply attributed to decreased secretion of ADP or ATP.

Taken together, the results from this study clearly underscore important roles for polyphosphate secreted from activated platelets in both hemostasis and thrombosis. The decreased aggregation seen in platelets from homozygous IP\(_6\)K1 knockout mice is particularly intriguing because a role in platelet aggregation has not previously been reported for polyphosphate. The availability of this mouse line for studying the consequences of severely reduced polyphosphate levels in platelets will allow a wealth of studies to investigate the biological roles of polyphosphates in mammals, no doubt beyond their currently appreciated contributions to hemostasis, thrombosis, and inflammation.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES


© 2013 by The American Society of Hematology

---

Transplants for the elderly in myeloma

Gareth J. Morgan\(^1\) INSTITUTE OF CANCER RESEARCH AND ROYAL MARSDEN HOSPITAL

In this issue of \textit{Blood}, Gay et al provide important new information that can be used to design future phase 3 trials.\(^1\)

They chose a dose of melphalan known to be tolerated in this age group and augmented its activity by using cassettes of treatment using novel agents during induction, consolidation, and maintenance and evaluated its activity and tolerability in the 65- to 75-year-old age group. It is clear that it is well tolerated, with minimal early mortality and is associated with good response and survival data. It is possible to compare these outcomes with representative historical data sets including the Medical Research Council (MRC) study where the overall survival (OS) in the nontransplanted group for melphalan-prednisone vs cyclophosphamide-thalidomide-dexamethasone was 30.6 vs 33.2 months, respectively, and for patients in the transplanted group >64 years of age was 53 months.\(^2\) In the Intergroup Français du Myélome (IFM) 99-06 study comparing melphalan-prednisone with melphalan-thalidomide-prednisone and with autologous stem cell transplant (ASCT) with 100 mg/m\(^2\) of melphalan, the OS in each group was 33.2, 51.6, and 38.3 months, respectively.\(^3\) Thus, the 5-year OS of 63% in the current study is good, using this novel sequential approach.
to treatment, which should now be evaluated formally against current standard approaches for this age group.

Maximizing cure rates by personalizing therapy is one of the major aims of modern myeloma treatment. With respect to achieving cure, one of the major prerequisites is the achievement of a stringent complete response (sCR) as assessed by multiparameter flow cytometry. It has been increasingly possible to achieve this aim in younger patients treated with ASCT where such sCRs are associated with optimum clinical outcomes.1 The integration of novel therapies into the context of ASCT has further improved overall and sCR rates and has changed the prevailing treatment paradigm which now comprises induction, transplant, consolidation, and maintenance treatment blocks. These blocks of treatment are delivered with the aim of sequentially reducing tumor bulk and incorporate the concept of using combinations of drugs incorporated into cassettes of treatment, which when combined have synergistic effects maximizing response rates. In addition, at each treatment phase, different cassettes comprising different combinations of drugs are given with the aim maximizing the chance of inducing apoptosis in resistant subclones and reducing the risk of relapse. More recently, the aim of maximizing responses has incorporated the concept of “maintenance treatment,” whereby ongoing treatment is given aiming to control the biology of residual clonal populations and killing myeloma stem cell populations coming into cell cycle.5,6

The incorporation of these ideas has revolutionized the treatment of younger patients, but it has come at the price of potentially increasing toxicity that needs to be managed. This is perhaps not an issue for the 40% of patients who develop myeloma before the age of 60, but for the majority of patients who develop myeloma beyond this age, toxicity is a significant issue. ASCT is considered the standard treatment of younger fit patients, but there is no consensus in terms of an age cutoff above which ASCT is contraindicated. The initial IFM study used 60 years as an age cut point, whereas the MRC VII study used 65 years.7,8 In subsequent studies, including Myeloma IX, the MRC group used doctor and patient preference to decide on treatment pathway and included patients up to the age of 73 years in the transplant strategy. In an analysis of this study based on 5-year age cohorts, it was clear that there were differences in survival for the 55 to 60, 60 to 65, and 65 to 70 year groups, but mortality was not an issue. Interestingly, although a small number of patients over the age of 70 were included in the study, none made it to the transplant procedure for a number of reasons, including failure to collect stem cells and doctor or patient preference, making 70 a pragmatic age cutoff above which a full dose of 200 mg/m² is generally inappropriate.2

The definition of an age cutoff of 70 years raises the issue of what is the best way of treating this age group, as well as younger patients who are considered too frail to receive a full dose of melphalan. One way of making high-dose melphalan more applicable is to reduce the dose. The standard dose of melphalan is 200 mg/m², which reflects the fact that 3 positive studies comparing transplant to standard therapy used this dose,8 whereas studies using lower doses were not associated with positive survival benefits.3,9 In a variation on the single dose of melphalan approach, a sequential 100 mg/m² approach has been evaluated and was found to be tolerable but again it did not improve survival.10

Conflict-of-interest disclosure: G.J.M. has participated in advisory boards for, received payment for lectures and development of educational presentations from, and received travel support from Celgene, Millennium, Novartis, Merck, and Johnson & Johnson.

REFERENCES
At this time, there is a void in the field of antibody–drug conjugates (ADC) targeting CD33 as a therapeutic option for treatment of AML after the voluntary withdrawal of gemtuzumab ozogamicin (GO) from the market. Even though CD33 is an antigen that is both considered to be expressed in more committed myeloid precursors and is not present in AML stem cells, the clinical relevance of CD33 as a target is validated by patients with AML in randomized clinical trials.

The reliable efficacy of drug conjugation with antibody and the greater stability of conjugate to avoid the exposure of non-target-expressing tissue to drugs can improve CD33 ADCs as therapeutic agents. The PBD dimer released after protease cleavage of SGN-CD33A causes DNA cross-linking and is capable of inducing cell cycle arrest and apoptosis. Engineered cysteine moieties at linker attachment sites allow more precise PBD dimer loading of antibody, thus improving predictability of payload delivery. The activity of SGN-CD33A requires CD33 expression, but its activity does not correlate with levels of CD33 surface expression. In vitro studies with SGN-CD33A showed approximately 3-fold more potency than GO shows against primary AML cells. What makes SGN-CD33A potentially interesting is that this ADC appears to have activity irrespective of the multidrug resistance phenotype and p53 status of AML cells. Additional in vivo studies using immune–competent isogenic mouse models of disseminated AML with relevant translocations/mutations and variable p53 backgrounds are needed to add valuable information to the current report. In addition, data regarding levels of “naked” PBD dimer in plasma after infusions are important, as this may have relevance with regard to nonspecific toxicity.

There is a distinct need in the field for CD33-based ADCs to quickly fill the void left by the withdrawal of GO from the market, and the rapid preclinical and clinical development of agents such as SGN-CD33A is needed.

Conflict-of-interest disclosure: The author declares no competing financial interests.
Transplants for the elderly in myeloma

Gareth J. Morgan