

Preface

Systemic cancer treatment led to increasing survival rates and even cures in an impressive number of tumor types within the last five decades, especially in patients with high-growth-fraction tumors benefitted from this development.

Autologous transplantation of bone marrow or peripheral blood hematopoietic stem and progenitor cells (PB HSC/HPC) following high-dose chemotherapy allowed an up to sixfold increase in dose intensity and was a further milestone enabling cure or long-term disease control in lymphoma, myeloma, and solid tumors. Introduction of cytokines (e.g., G-CSF) in the 1980s significantly improved PB HSC/HPC collection for blood stem cell transplantation. Since then, no significant progress beyond chemotherapy-supported and cytokine-based HSC/HPC mobilization had been made.

In the early 1990s, AMD3100, now plerixafor—chemically a bicyclam—was originally developed as an anti-HIV drug; the chemokine receptor CXCR4 was identified as the target for plerixafor. In the late 1990s, CXCR4 was discovered as a crucial factor for HSC/HPC retention in the bone marrow. As with a considerable number of drugs, serendipity played a decisive role in elucidating the potency of plerixafor for HSC/HPC mobilization: in HIV-infected patients plerixafor induced an unexpected dose-dependent leukocytosis and in healthy volunteers it was found that these increased peripheral blood mononuclear cells were enriched by CD34⁺ HSC/HPC. Subsequently, it became clear that the number of patients who can profit from PB HSC/HPC transplantation could be increased since older patients and poor mobilizers following standard mobilization strategies (G-CSF, chemotherapy) also showed increased numbers of circulating CD34⁺ HSC/HPC after addition of plerixafor. This action and the synergism of plerixafor with G-CSF led to the clinical approval of plerixafor as a first in class compound for mobilization of HSC/HPC. The amount of HSC/HPC mobilization and the rapid kinetics compare favorably with classical mobilization protocols and are a quantum leap for hard-to-mobilize patients who now become eligible for potentially curative treatment.

Increased HSC/HPC mobilization by compounds interacting with their adhesion in bone marrow niches is a substantial step toward improvement of PB HSC/HPC transplantation, so that meanwhile, further compounds with potent mobilizing capacity were developed and are presently in clinical phase I and II trials.

An exciting new role for CXCR4 inhibitors emerged by the discovery that cells of different tumor types—leukemias and solid tumors—express CXCR4 as well and that SDF-1–CXCR4 interaction is involved in adhesion and movement of cancer cells. Although there are concerns regarding side effects to normal cells, it is a fascinating idea for oncologists that mobilization of tumor cells (e.g., by interruption of the SDF-1–CXCR4 axis) could someday eliminate the threat of minimal residual disease, since mobilization of MRD cells from protective niches to the blood might increase their chemotherapeutic sensitivity.

Last but not least, use of CXCR4 antagonists in tissue repair and in inflammatory diseases has led to exciting new approaches that will be reviewed in this book, too.

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Novel Developments in Stem Cell Mobilization

Focus on CXCR4

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