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Proceedings from the National Cancer Institute's Second International Workshop on the Biology, Prevention, and Treatment of Relapse after Hematopoietic Stem Cell Transplantation: Introduction

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Advances in the science and technology of hematopoietic stem cell transplantation (HSCT) have led to improved transplant outcomes almost exclusively through the reduction of transplant related mortality. Despite continued progress, there has been minimal change in the incidence of post-transplant relapse, which remains the leading cause of death after HSCT. [1] To address this problem, the National Cancer Institute (NCI) organized two international workshops on this subject. The goals of the first workshop, held in 2009, were to review the state of the science and to generate recommendations for research efforts. [2–10] Three major initiatives for coordinated research were proposed: 1) To establish multicenter networks for basic, translational, epidemiologic and clinical research; 2) To establish a network of biorepositories for the collection of samples before and after HSCT to aid in laboratory and clinical studies; and 3) To refine, implement and study proposed definitions for disease-specific response and relapse and for monitoring of minimal residual disease (MRD). [10] The overarching goals of the second NCI workshop held in 2012 were to advance those recommendations. (Table)

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To facilitate the development and coordination of multicenter studies and post-transplant relapse clinical trials networks, a Protocol Planning Committee, three Protocol Development Teams (Biology, Prevention and Treatment) and multiple Study Teams were assembled during the planning and preparation stages of the second workshop. Protocol concepts were developed in advance and presented at the workshop for further refinement. Additional aims of the second workshop were to update the current state of the science and to provide a forum for the presentation and review of research related to the biology and clinical studies of relapse. Attendees included 180 individuals from 9 countries. Fifty-seven scientific abstracts were presented as part of the Scientific-Education Program. The agenda, presentations and abstracts are available on the workshop website. [https://ccrod.cancer.gov/confluence/display/2012NCIRelapse/Home]

The workshop featured nine keynote presentations, summaries of which follow in three manuscripts. In Part I – "Biology of Relapse after Transplantation," recent advances in understanding host, disease and transplant-related contributions to relapse are reviewed including the biology of the therapeutic graft-versus-malignancy effect, immunologic homeostasis and reconstitution, the tumor microenvironment and clonal escape. Part II – "Relapse Prevention using Novel Agents and Immunomodulatory Strategies" represents an extension of the initial workshop efforts into the arena of autologous transplantation. The role of novel agents and immunomodulatory strategies in management of relapse of multiple myeloma are discussed, with broader consideration of areas relevant for relapse of other malignancies and after allogeneic transplantation including tumor vaccine strategies, approaches to overcome tumor-associated immunosuppression and tolerance, and natural killer cell biology and therapies. Part III – "Prevention and Treatment" addresses newer agents, donor lymphocyte infusions and novel cellular therapies to enhance graft-versus-tumor activity.

There is reason for optimism in the study and treatment of post-transplant relapse. Whole genome sequencing has opened an entirely new approach to study malignant progression and relapse. [11–12] MRD detection and early intervention have proven beneficial in specific diseases. [7–8] A growing number of clinical trials focused on relapse after HSCT are in development or underway. The results of the Cancer and Leukemia Group B (CALGB) 100104 and the Intergroupe Francophone du Myélome (IFM) 99-02 trials should encourage us to fulfill the main goal of this second workshop, which is develop a portfolio of treatment, prevention and tissue acquisition protocols to move the field forward and to firmly establish the required infrastructure to perform such work. That the relatively simple addition of lenalidomide after an autograft significantly increases the post-transplant progression-free and event-free survival rates for individuals with myeloma [13–14] suggests that additional strategies will be effective in other diseases and transplant settings. [15–17]

Although time and resources are limited, it is critical that the scientific community vigorously pursues studies of the biology of post-transplant relapse and approaches to combat relapse after HSCT. It will only be through concerted and coordinated efforts that significant improvements will be achieved in the treatment and prevention of this primary cause of death after transplantation.

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TABLE

Goals of the National Cancer Institute's Second International Workshop on the Biology, Prevention, and Treatment of Relapse after Hematopoietic Stem Cell Transplantation

- **I.** Protocol Development Goals
  - **A.** To establish multicenter networks for basic, translational, epidemiologic, and clinical research
    - **1.** Leverage and integrate existing networks, consortia, organizations and agencies
    - **2.** Align investigators and institutions with established research interests
    - **3.** Promote ongoing research activities
  - **B.** To help address key issues
    - **1.** Funding
    - **2.** Infrastructure
    - **3.** Access to new agents
    - **4.** Trial design, statistical challenges
    - **5.** Central lab monitoring for novel endpoints and biomarkers
    - **6.** Data collection and reporting
- **II.** Biorepository Establishment Goals
  - **A.** To facilitate the establishment of a network of biorepositories for the collection of samples before and after HSCT to aid in laboratory and clinical studies
  - **B.** To promote the collection of human samples
    - **1.** Pre- and post- transplant malignant cells
    - **2.** Allograft
    - **3.** Blood at set time points post-transplant and at relapse
  - **C.** To establish standards for collection, storage, utilization and distribution
  - **D.** To help coordinate investigators and institutions with established repositories
- **III.** Disease-Specific Response and Relapse Definitions and Monitoring Goals
  - **A.** To refine, implement and study proposed definitions for disease-specific response and relapse and for monitoring of MRD
  - **B.** To incorporate sensitive evaluation methods into clinical trials
    - **1.** Determine clinical relevance of MRD surveillance in specific diseases
    - **2.** Assess the impact of interventional strategies after detection of MRD
  - **C.** To work towards increased data collection, standardization and reporting specifically related to relapse after HSCT

HSCT: hematopoietic stem cell transplantation; MRD: minimal residual disease