2004 Forbeck Focus Meeting: Fertility and Reproductive Issues in Survivors of Childhood Cancer

Organizer: Charles Sklar, MD, Memorial Sloan-Kettering Cancer Center

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Focus: Advances in the treatment of childhood cancer, including combination chemotherapy, radiation therapy, surgery, and stem cell transplantation have resulted in markedly improved survival rates for many patient-groups. Currently, the overall five-year survival rate is in excess of 70%. However, with these advancements, cancer survivors now face the long-term consequences of treatment with intensive, multimodality therapies. Impaired fertility and compromised reproductive function are, unfortunately, common sequela for both men and women exposed to chemotherapy, surgery, and/or radiation. Understandably, infertility may have profound psychological effects on survivors, particularly as they reach young adulthood. The risk of infertility varies considerably and is influenced by a variety of factors such as age and sex of the subject, type and dose of chemotherapy, and dose and field of radiation. Such uncertainty only intensifies and complicates the already difficult tasks all young individuals face as they mature: forming intimate relationships, having a family, and embarking on a career. Critical gaps currently exist in our understanding of the basic mechanisms involved in chemotherapy- and radiation-induced germ cell loss. Options for preserving or protecting fertility prior to the initiation of cancer therapy are quite limited. For sexually mature males, cryopreservation of semen is well established and effective. Transposition of the ovaries out of the radiation field is also a viable strategy for the small number of females who require only focal abdominal-pelvic irradiation. However, for pre- and peri-pubertal individuals of both sexes and most sexually mature females, few if any proven options exist. Recently, harvesting and cryopreservation of ovarian tissue has become technically feasible. Cryopreservation of immature male testicular tissue or germ cells remains a theoretical possibility. While the data to date do not indicate a significant increase in birth defects or cancer in offspring of cancer survivors conceived by natural means, the long-term risks to the offspring conceived using the newer techniques of assisted reproduction are as yet unknown. We find ourselves at a critical juncture in the area of fertility and cancer survivors. Rapid advances in basic biology and various reproductive technologies mean that in the very near future new treatment options will become available for both fertility preservation and restoration. While such innovations offer exciting new alternatives for our patients, they also raise very serious health and ethical concerns. Collaboration and cross-talk between clinicians (medicine, pediatrics, psychology, bioethics), basic scientists (molecular biologists, cell biologists, animal scientists), and epidemiologists (population statistics) are essential if we are to move forward in ways that are scientifically sound, medically safe, and ethically grounded. A Forbeck Symposium would be an ideal setting for such discussions and interchanges.

Outcome Report: Dr. Dolores Lamb from the Baylor College of Medicine presented on normal testicular development and recent advances in our understanding of the complex anatomy of the human testis. She reviewed information on the process of normal spermatogenesis, the blood-testes barrier, normal germinal and supportive cell interactions and the normal hormonal milieu within the testis. There was
much discussion on the implications of the blood-testis barrier in protecting germ cells from the toxic effects of systemic chemotherapy.

Dr. Alan Schneyer from the Massachusetts General Hospital and Harvard Medical School presented on the inhibins and activins. He emphasized the importance of activins in the regulation of normal germ cell development and its role in the local communication systems that regulate gonadal function. The clinical value of inhibin B measurement as a maker of male germ cell failure was discussed and the need for additional work in this area were emphasized. Dr. Richard Kolesnick from the Memorial Sloan-Kettering Cancer Center presented on strategies to protect germ cells from apoptosis. Data were presented on the sphingomyelin pathway and its role in oocyte apoptosis. New studies in C. elegans demonstrate that ABL-1 distinguishes proapoptotic signals triggered by two different DNA-damaging agents. There was much discussion on the potential clinical implications of interfering in the normal process of cell death, particularly when mutagenic damage may have occurred.

Dr. Marvin Meistrich from the M.D. Anderson Cancer Center addressed the topic of enhancement of recovery of spermatogenesis after cytotoxic therapy by suppressing endogenous testosterone production. He reviewed data from several animal models that demonstrate that reducing intratesticular testosterone has the ability to enhance differentiation of surviving stem cells. Additionally, this strategy enhances the ability of transplanted stem spermatogonia to colonize and differentiate in busulfan-treated testes. The discussion included the lack of efficacy of this approach in the human and non-human primate and the need for further data to allow further elucidation of the mechanism of this enhancement in the animal.

Dr. Kuluk Oktay from the Weill Medical College of Cornell University spoke on the options for fertility preservation in the prepubertal female. Areas discussed included protection by means of gondatropin suppression, oocyte freezing, and ovarian cryopreservation and transplantation. The world’s experience with these various techniques was reviewed. Recent advances in ovarian tissue cryopreservation were the main focus of the discussion. Differences between the European and North American approaches and the lack of good clinical guidelines were emphasized. All participants agreed that there is a need for closer collaboration between Reproductive Medicine units and Pediatric Oncologists.

Dr. Stefan Schlatt from the University of Pittsburgh discussed techniques for germ cell preservation in the prepubertal male. The focus of his presentation was on autologous germ cell transplantation and autologous/xenologous testicular grafting. In animals, investigators have recently shown that xenografting of neonatal testicular tissue from a variety of species has resulted in differentiation to the level of complete spermatogenesis. It was emphasized that these techniques remain highly investigational as the overall safety and efficacy is unknown when applied to the human. Dr. Roger Gosden, from the Weill Medical College of Cornell University, presented on the topic of assisted reproduction for the infertile female. He outlined the options available for fertility preservation including embryo/oocyte banking, ovary banking, in vivo protection, and donor eggs/embryos adoption. In addition, he discussed the issues and considerations relating to unanswered questions in the area of assisted reproduction, current and future research, and the decision-making process for physicians and patients/families.

Dr. Peter Schlegel of the Department of Urology at Cornell University discussed topics related to the assisted reproduction for the infertile male. A focus of his presentation was on approaches for retrieval of sperm from patients with limited spermatogenesis, which included surgical strategies to
optimize the identification of sperm-producing tubules and sperm retrieval. He described current techniques for microdissection of the testicular parenchyma and the success rates achieved among a series of men with cancer therapy-induced gonadal dysfunction.

Dr. Andre van Steirteghem of the Centre for Productive Medicine at the University of Brussels addressed the topic of outcomes of assisted reproduction. He provided a brief historical perspective to assisted reproduction and then discussed the level of information that is currently available. Dr. van Steirteghem emphasized the limited number of well-designed outcome-based studies and the importance of ongoing research. Issues including methodological limitations of prospective studies of offspring to assess congenital abnormalities/health-outcomes, genetic counseling and the impact of multiple pregnancies were all discussed.

Dr. Les Robison, from the Department of Pediatrics and the Cancer Center at the University of Minnesota, provided an overview of childhood cancer survivors, emphasizing the marked and relatively rapid improvements in survival rates over the past three decades. He outlined the spectrum of issues faced by adult survivors of childhood and adolescent cancers, including fertility and health of offspring. A primary conclusion was that there must be ongoing research to better define those survivors who are at highest risk for decreased fertility. Dr. Charles Sklar, from the Department of Pediatrics at Memorial Sloan Kettering Cancer Center, presented recent unpublished results of his research on premature menopause among adult survivors of childhood cancer. His data, from the Childhood Cancer Survivor Study cohort included more 2800 long-term survivors, demonstrates that survivors have a 13-fold increased incidence of non-surgical premature menopause compared to a cohort of sibling controls and the identification of independent risk factors. Further discussion focused on the implications of an increased risk of premature menopause for cancer survivors.

Dr. Stephen Shalet, Professor of Endocrinology at the Christie Hospital, University of Manchester, summarized the data regarding the impact of chemotherapy and radiation on fertility among male pediatric and adolescent cancer patients. He detailed the specific chemotherapeutic agents associated with gonadal toxicity emphasizing the drug- and dose dependent nature of the long-term effects. Importantly, he detailed the potential for late recovery following chemotherapy-induced damage to the germinal epithelium. Professor Shalet also described the issues related to radiation-induced damage to the male testis, again detailing the time-dependent nature of spermatogenesis following radiation exposure. Dr. Leslie Schover, from the Department of Behavioral Science at MD Anderson Cancer Center discussed the psychosocial aspects of infertility after pediatric cancer, including knowledge gaps and communication issues that represent barriers to implementing possible preventive measures. She detailed the emotional, clinical and technologic components of fertility-related decision making among patients and parents. Dr. Schover presented examples of web-based resources that are being developed to aid cancer patients and families with fertility issues. Dr. Jeff Kahn, Director of the Center for Bioethics at the University of Minnesota, discussed the ethical issues associated with assisted reproduction and germ cell preservation among children diagnosed and treated for cancer. Within the context of donation and preservation of germ cells, he described and discussed the risk-benefit considerations, issues of informed consent and control of stored tissues. The discussion of ethical considerations relating to assisted reproductive technologies (ART) focused not only on the risk-benefit issues, but also topics associated with life expectancy of the survivors, disposition of gametes/embryos and access to unused tissues.

Lastly, Dr. Kahn raised points regarding defining ART-related procedures as research versus innovative therapy, as well as the role of federal funding of research and involvement of third party payers.
The participants were all in agreement that there was a great deal of additional research needed both to better understand the underlying pathophysiology of cancer treatment induced germ cell death but also to improve the safe options available to cancer patients about to embark on treatments associated with a high-risk of infertility. It was quite clear that this Forbeck conference generated a tremendous amount of enthusiasm and thought. For many participants it helped crystallize areas that need further exploration and clarification. For all involved, the meeting was viewed as a tremendous success and a model for future meetings and collaborations.

Quotes from Participants:

“Our conference this past weekend was (in the words of one of the attendees) “a resounding success.” There was an amazing amount of dialogue and interchange. Several of the investigators actually began collaborations during the conference, while many others expressed a desire to pursue mutual areas of interest in the future. The setting was ideal and even the weather was nearly perfect!”

- Charles Sklar, MD, Memorial Sloan-Kettering Cancer Center