General discussion
New horizons, new challenges

Fanconi anemia (FA) is a rare, hereditary disorder characterized by congenital malformations, bone marrow failure (BMF), endocrine abnormalities and a high risk of developing malignancies, mainly acute myeloid leukemia (AML) and squamous cell carcinoma (SCC). The only curative treatment for BMF in FA is hematopoietic stem cell transplantation (SCT).

This thesis has addressed genetic, clinical and care aspects of FA in the Dutch setting. It shows that in the past 15 years improved diagnostics and SCT innovations have dramatically extended the lifespan of FA patients. Subsequently, more patients will reach adulthood and will be confronted with other life threatening complications of their disease, such as the development of SCC in early adulthood. Furthermore, FA patients are increasingly being referred to physicians involved in adult healthcare, who have, in general, limited experience with this rare, complex disorder.

This thesis underlines that FA no longer is only a disease of childhood and care for FA needs to grow out of infancy as well. In this general discussion, we describe the future perspectives, challenges and opportunities in caring for patients with FA.

The Dutch FA mutation, a mild variant?

Our study showed that FA is more prevalent than we initially anticipated. At the beginning of this research project approximately 30-35 FA families were known. To date, 137 patients have been identified of whom 84 are currently alive. Analysis of the national Dutch FA cohort confirmed that most patients belong to the FA-C genetic subgroup and that the c.67delG FANCC mutation, due to a founder effect, is the most prevalent FA mutation in the Netherlands.

Patients with the Dutch mutation are considered to have a mild phenotype, especially in terms of congenital abnormalities, but data on course of disease are scarce. To improve care, the course of disease in this patient group needed to be studied. We confirmed that patients with homozygous c.67delG mutations in the FANCC gene indeed have no major congenital abnormalities. Nevertheless, a significant number of these patients developed life threatening BMF and malignancies, mainly SCC. Therefore, we recommend that treatment guidelines, including stringent and lifelong screening for BMF and cancer, should not be liberalized for this specific patient group. Obviously we have to be careful with the interpretation of genotype-phenotype correlations. The number of patients and families is generally small, and FA is a heterogeneous disease. Moreover, one event such as bone marrow failure and treatment thereof, may impact other events such as cancer development.

The Dutch FA patient registry is a valuable tool to follow the course of disease of FA patients
in the Netherlands, to evaluate results of treatment modalities over time and to answer future research questions. Effort should be made to continue and enhance the registry by including newly diagnosed patients and perform yearly follow-up of included children and adults.

**Stem cell transplantation for FA: not if but when?**

We have shown that current SCT results for FA patients transplanted with matched related as well as matched unrelated donors are excellent. Nonetheless, challenges remain in specific FA subgroups. The current Dutch conditioning regimen appears to be insufficient to ensure engraftment after haplo-identical donor SCT. High numbers of infused CD34+ cells and more intensive conditioning regimens seem to be required in this specific group. Furthermore, our study underlines that the chances of success are clearly higher when patients are transplanted at a young age. Since outcome of SCT in young FA patients is significantly superior to the outcome in adult patients, it could be questioned whether or not all FA patients should be transplanted at young age. Should we proceed to SCT directly after diagnosis or only in case of stringent conditions, such as transfusion-dependency? In this context, young adolescent FA patients with mild BMF are facing a difficult decision. With increasing age their chances of a favorable outcome after SCT will decline, but at the same time the SCT related morbidity and mortality are substantial. Furthermore, SCT-related complications such as GVHD increase the risk of life threatening post-transplant malignancies. It remains important to only expose FA patients to SCT if and when necessary, especially since not all FA patients will develop BMF. Therefore, SCT should not be performed unnecessarily early, but if inevitable, it should ideally be performed before the age of 15 years. The decision when to proceed to SCT should be made by combining the evolution of hematological parameters, evaluated by monitoring of peripheral blood and bone marrow, donor availability and patient's considerations. Decision models are being developed to support decision making. For adult FA patients who need SCT, evaluable conditioning regimens should be formulated, based on the experience with reduced doses of busulfan or irradiation. Evaluation of these regimens by means of a HOVON or EBMT adult FA SCT registry is of great importance. In general, long-term follow up of transplanted FA patients remains necessary to evaluate SCT-related morbidity and SCT-induced cancer risk of current and new conditioning regimens.

**Head and neck squamous cell carcinoma in FA: the main challenge in the years to come**

In this thesis we have shown that noninvasive LOH screening is a promising method to identify oncogenetic changes in FA patients. We detected LOH in nearly 10% of the sampled
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FA patients and showed that LOH is significantly associated with HNSCC. Further studies are needed to study the feasibility of noninvasive genetic screening in the clinical setting. In the meantime, it could be considered to perform noninvasive genetic analysis of suspect visible oral lesions. If oncogenetic changes are found, the frequency of screening should be increased in order to carefully follow the evolution of the visible lesions and to proceed to invasive diagnostics or treatment in time.

During the study we noticed that the presence of donor DNA in epithelial brushes of transplanted FA patients interfered with the LOH analysis. Since transplanted FA patients are at even higher risk of developing HNSCC, it is absolutely necessary to develop more sensitive screening assays.11 Next generation sequencing methods may have a higher sensitivity.15 Nevertheless, the presence of leukocyte DNA will also influence these methods. HNSCCs in FA patients are most often located in the oral cavity.16,17 Of interest, in our FA cohort 4 of the 5 patients with oral cancer had SCC of the gingiva. The gingiva seems to be a high risk site for oral cancer in FA and we advise head and neck surgeons and ENT doctors to thoroughly examine the gingiva during the 3-monthly screening.

To find optimal preventive and curative strategies for HNSCC in FA will be the most important challenge in the years to come. To date, experience with HNSCC in FA is shared insufficiently. Based on scarce literature and personal communication during meetings and conferences it is clear that treatment results of individual FA patients with HNSCC and other SCCs are disappointing.17,18 Morbidity is high, tumor recurrences are common and overall survival is poor.16,18 Collecting and publishing information on HNSCC in FA, and especially the effect and toxicity of chemotherapy and irradiation, is necessary to increase knowledge on cancer treatment in FA. It is also of great importance to gather the experience with new developments in treatment of HNSCC in FA. The use of carefully dosed irradiation, instead of the conventional restraint to use irradiation, as well as radioprotective antioxidants to decrease toxicity, are being explored.18,19 Furthermore, targeted molecular therapy with cetuximab, an epidermal growth factor receptor-specific antibody used in treatment of sporadic HNSCC, could be of interest for FA patients with HNSCC.20

Treatment guidelines for cancer in FA are currently not available, possibilities to treat cancer in FA are limited and FA is a very rare disease. Consequently, centralizing treatment of FA patients with cancer is essential to improve outcome. In addition, developing a consultative, international expert-platform for physicians and researchers to collect and share experience with the treatment of cancer in FA would be of great importance.

Healthcare for Dutch FA patients: room for improvement!

FA is no longer only a disease of childhood. Nearly 40% of the current Dutch FA cohort is aged 18 years or older. This directly reveals an important challenge, since care for adult
patients with FA still needs to be developed. Furthermore, new questions, raised as a consequence of the increased lifespan of FA patients, need to be addressed.

The majority of Dutch FA patients are currently treated in Dutch University Medical Centers. We have shown that a significant part of the Dutch FA patients receive suboptimal care, despite the availability of national FA treatment guidelines. In addition, the transition process from pediatric to adult healthcare proves to be difficult. Concentrating and centralizing healthcare is essential to improve care for very rare, complex diseases such as FA. Special attention for transition is needed to bridge the current gap between pediatric and adult healthcare. In the Netherlands adult healthcare is not organized to provide comprehensive care for rare, complex, multisystem diseases such as FA. A multidisciplinary healthcare team that provides lifelong, comprehensive care for children and adults with FA, including regular screening of (pre)cancer, needs to be developed. Furthermore, a (inter)national consultative network of healthcare professionals and researchers should be established to share data on course of disease and treatment results, and provide a basis for future research.

To optimally organize care for FA, adoption of proven effective initiatives for other rare diseases should be considered, such as comprehensive care departments like the Sylvia Toth Center or the Van Creveld Clinic for hemophilia and the aftercare system for survivors of pediatric cancer (late effect screening networks). Furthermore, to improve transition from pediatric to adult healthcare, transition protocols and transition programs, such as available for cystic fibrosis or pediatric rheumatic diseases could be followed.

Optimal cooperation between patients, their organizations, multidisciplinary healthcare teams and scientists is of great importance. In the past few years collaboration between FA healthcare professionals, FA researchers and the Dutch FA patient organization has led to several valuable projects, such as the development of an FA website and an informative FA brochure for general practitioners. These tools will empower patients to obtain and share information about their disease and take control of their healthcare needs. In the coming years, collaboration between physicians, patients and scientists will further improve care for children and adults with this complex disorder.
References


