Prediction and prevention of infectious complications in children with cancer
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Ungibonise yank' indlele
"you will show me the way"

Chapter

Discussion
The first part of this thesis discussed studies on predicting the course of infectious complications in the child with cancer, and the second part presented studies on preventing infection in which two systematic reviews were presented. Therefore the discussion will be divided in
a) Predictors of the clinical course of infection
b) Prevention of infection
At the end of the discussion an overview of the implications for clinical practice and proposals for future research will be given.

a) Predictors of the clinical course of infection

Chapters 3 and 4

With the increasing intensity of chemotherapy the cancer patient remains susceptible to infectious complications. In the introduction emphasis has been given to the various risks of the neutropenic patient for infection. Increased understanding of these various risks have led to risk assessment models which are now applied in adult patients\textsuperscript{1,2}. These risk-assessment models have also been developed for children. Orudjev et al\textsuperscript{3} reported on all pediatric trials done on risk-assessment. Twenty-seven prospective trials were identified and five reviews. So far no internationally validated risk prediction rule is available for children. Deducted from the best available evidence one could define the low-risk prediction rule as follows: “The child with low-risk febrile neutropenia is clinically well and afebrile within 24-96 hours of therapy and has evidence of marrow recovery with a rising phagocyte count”\textsuperscript{3}. Empirical therapy will be instituted in the hospital and decisions can be made to switch to oral antibiotic therapy after initial intravenous therapy. Prospective validation of the low prediction rule is necessary prior to implementing this rule in pediatric oncology practice. Next to clinical parameters biochemical parameters can be used as diagnostic tools to predict the course of the severity of an infection\textsuperscript{46}. In this thesis we concentrated on predicting the course of one severe complication in oncology patients, i.e. neutropenic enterocolitis.

In Chapter 4 we presented a prospective single center study gaining insight in the incidence and pathogenesis of neutropenic enterocolitis in pediatric oncology patients. In this study twenty-five patients were included (mean age 7.1 years) with suspected neutropenic enterocolitis. Eight patients (32%) needed intensive care treatment, 3 (12%) patients died. Predictors of a severe clinical course of the enterocolitis were an increased serum IL-8 (>1000 pg/mL) and an increased serum CRP (>150 mg/L). Relative risks for admission to ICU was 11.3 (95% CI 1.6 to 77.9) for elevated IL-8. Therefore IL-8 on the first day of suspected neutropenic enterocolitis can be used as a predictive marker.

In future studies it is important to try and prevent this severe complication.
If you can prevent severe mucositis, this will most likely lead to less gastrointestinal damage and therefore a decrease in the incidence of neutropenic enterocolitis.
A phase III cross over designed study has recently started in 2 pediatric oncology centers (Sophia Children’s hospital, Rotterdam and Emma Children’s Hospital, Amsterdam) administering Transforming Growth factor β (TGF-β) as a mouthwash and added to the food as an oral solution to pediatric oncology patients who are expected to develop a severe mucositis on the basis of the chemotherapy given (Principal investigator Prof. R. Pieters: Sophia Children’s Hospital, Rotterdam). TGF-β is a growth factor present in many mammalian tissues. In vivo studies have shown that the mucous membranes stabilize after adding TGF-β, because TGF-β can inhibit the proliferation of epithelial cells. Chemotherapeutic drugs target rapidly proliferating cells. The capacity of TGF-β to down regulate the proliferation of the oral and gastro-intestinal epithelial cells makes this growth factor of interest in possibly decreasing the chance for severe mucositis in oncology patients. This can consequently lead to decreasing the incidence of neutropenic enterocolitis.

Another way to improve the human intestinal epithelial barrier function might be the introduction of probiotics in an early stage of the treatment. Probiotics have been defined as living organisms in food and dietary supplements which upon ingestion improve the health of the host beyond the inherent basic nutrition. In neonatal necrotizing enterocolitis interest has been shown in the administration of Bifidobacterium infantis and lactobacillus acidophilus. Lactobacillus appears to have protective immunomodulating properties inducing a Th2 response. And Lactobacillus have the ability to inhibit the adhesion of pathogenic bacteria to the intestinal wall. The pathogenesis however in cancer patients is different, the interaction of chemotherapy, antibiotics and damage to the gastro-intestinal barrier may be more difficult to influence with probiotics, this makes the application of probiotics uncertain.

It will not always be possible to prevent neutropenic enterocolitis. Therefore attention needs to be given to the patients who are predicted to develop a severe neutropenic enterocolitis using biochemical markers like IL-8 and CRP. Patients have a higher chance to recover if granulocytes are present. A future intervention study could focus on administering granulocyte-transfusions. For many years this has not been advocated because of the limitations in collecting adequate doses of leukocytes from healthy donors by steroid mobilization. The development and use of granulocyte colony stimulating factors to stimulate normal donors has generated renewed interest in granulocyte transfusions. The yield of leukocytes collected from normal donors is high, this could improve outcomes in patients with severe infections and severe neutropenia. A Cochrane systematic review has recently been published on the use of granulocyte transfusions in neonatal sepsis. Four RCT’s were identified. From these trials there is inconclusive evidence that the use of granulocyte transfusions leads to a reduction in morbidity and mortality.

A well designed randomised clinical trial is necessary to establish granulocyte transfusions as a viable therapeutic modality in the treatment of severe bacterial and fungal infections in patients who are deeply neutropenic.
MBL and prediction of the course of infections

If biochemical markers are going to be used in risk assessment models it will become very important to understand the mechanisms of the innate immune system. This immune system plays a critical role in the first few days of infection. Why some individuals always develop infections and others don’t might be linked to genetic differences $^{14}$. For instance MBL deficiency has been linked to longer febrile neutropenic episodes, and in other studies to more severe infections.

In Chapter 3 a pilot study is presented evaluating the role of mannan-binding lectin deficiency (MBL) in pediatric oncology patients with neutropenic fever. Twenty four patients were prospectively followed during an episode of febrile neutropenia. The incidence of MBL exon-1 gene mutations and MBL-deficiency ($<800 \mu g/L$) was 32.5%. However, no correlation was found with either the severity or frequency of the infections, although a trend was found towards a longer duration of neutropenia in the MBL-deficient group of patients. If we used the cut-off value of 1000 $\mu g/L$ (calculated with a ROC curve) there was a trend towards more bacteremia’s 37.5% in the MBL insufficient group compared to 13.3% in the MBL sufficient group. We evaluated a small cohort of patients, and results might change if the cohort is extended. Kilpatrick et al $^{15}$ found no relation with severity or frequency of infections in a large group of adult oncology neutropenic patients. These patients might be too neutropenic, therefore the effect of MBL deficiency could be overshadowed. This might also be the case in our studied cohort. Therefore it is important to extend the cohort to ultimately define a group who will benefit most from substituting MBL, possibly the patients who receive their induction-period of chemotherapy.

The possibility is already present to substitute MBL. In 1995 the Statens Serum Institut (SSI, Copenhagen, Denmark) began developing MBL concentrated plasma product, from pooled human plasma for the treatment of patients with frequent infections associated with MBL-deficiency. A phase I trial has been completed investigating the safety and pharmacokinetics of MBL in 20 adult MBL deficient volunteers (see product information SSI, Denmark, Kopenhagen). This was completed without side-effects being reported and good tolerability. Now a small phase II trial has been designed and approved by the ethical committee to find evidence in 12 MBL-deficient pediatric oncology patients for the correct prediction of plasma levels of MBL, to confirm the dosage regimen needed to reach the required MBL plasma level, and reconfirm the safety and lack of side-effects (Principal Investigator: Prof. T. Kuijpers. CLB Amsterdam). Together with the data from the extended observational cohort study, this will gather the data needed to decide on a prospective randomised placebo-controlled phase III efficacy study in pediatric oncology patients with MBL replacement therapy.
b) Prevention of infection

Chapters 5, 6 and 7

Long-term tunnelled central venous catheters (TCVC) are increasingly used in oncology patients. Infections are a frequent complication of TCVC (Groeger, 1993, 206: Press, 1984, 189). These infections are mostly caused by Gram-positive bacteria (Mermel, 2000, 391). The aim of the systematic review as described in Chapter 5 was to evaluate the efficacy of antibiotics in the prevention of early Gram-positive TCVC infections. MEDLINE, EMBASE, and the Cochrane Controlled Trials Register were searched up to July 2003. All randomized controlled trials (RCT) evaluating prophylactic antibiotics prior to insertion of the TCVC, and RCT's evaluating the combination of an antibiotic and heparin to flush the TCVC were included. Both pediatric and adult oncology patient trials were selected. A total of 9 trials with 529 patients were included. Four reported on vancomycin/teicoplanin prior to insertion of the TCVC compared to no antibiotics, and 5 on flushing of the TCVC with a vancomycin/heparin solution compared to heparin flushing only. Both antibiotics prior to insertion of the catheter compared to no antibiotics and flushing the TCVC with antibiotics and heparin showed a significant reduction in the number of Gram-positive TCVC infections. The respective Odds ratio's were [OR]=0.46; 95% confidence interval 0.24-0.91 and [OR]=0.43, 95% CI 0.21-0.87). In oncology patients who need a TCVC and are at high risk for Gram-positive infections it is justified to use the above interventions. This should be implemented in clinical practice, especially in patients where the expected baseline infection-rate exceeds 10%, such as hematological patients during induction-phase of therapy and autologous and allogenic transplant patients.

Other preventative strategies to reduce catheter-related infections have so far been restricted to short-term non-tunnelled catheters. Studies involving antimicrobial/antiseptic impregnated catheters have all been performed in adult patients using non-cuffed catheters. Two meta-analyses have been performed on the use of chlorhexidine/silver sulfadiazine on the external luminal surface of the catheter 16,17. The studies analyzed showed a reduction in catheter-related bloodstream infections with a relative risk of 0.4. The benefit was realized in the first 14 days of placement of the catheter. Resistance to the chlorhexidine-silver sulfadiazine catheter has not been demonstrated in clinical studies. Newer generations of these catheters now coat the external surface with three times the amount of chlorhexidine and sulfadiazine and the internal surface is only coated with chlorhexidine. Results have shown that prolonged anti-infective activity provides improved efficacy in preventing infections 18. These catheters may be recommended in patient populations in which the infection-rate exceeds 3.3 per 1000 catheter days 19. A more recent alternative is to impregnate catheters with minocycline /rifampin. This has been shown to be 12 x more effective than the first generation chlorhexidine/sulfadiazine impregnated catheters 20, however no trials have been done comparing this catheter to the second generation chlorhexidine /sulfadiazine ones. This catheter does however seem
promising in patients with an expected duration of the catheter of 3 weeks. So far these strategies can not be used in long-term tunnelled catheters.

Other ways to prevent infection in cuffed catheters is the use of ionic silver in subcutaneous collagen cuffs attached to the central venous catheter\(^{21}\). The ionic silver provides antimicrobial activity and the cuff is a mechanical barrier to the migration of micro-organisms along the external surface of the catheter. However, this model is not very effective in reducing catheter related bloodstream infections in catheters that need to be in place for at least 3 weeks\(^{22}\). Segura et al\(^{23}\) introduced a new hub model to decrease endoluminal catheter contamination and catheter-related sepsis. This hub consists of a closed chamber containing 0.2 ml 3% iodinated alcohol (6 mg iodine). In this RCT the incidence of catheter related sepsis decreased with the use of this system in short-term catheters. No trials have so far been performed with this new hub in long-term tunnelled central venous catheters. Features of concern for long-term tunnelled central venous catheters are the iodine stability and the long-term hub concealment.

An alternative method of treatment of central venous catheter related infections is the use of antibiotic-lock therapy, first reported by Messing et al\(^{24}\), this is the introduction of a concentrated antibiotic solution into the catheter to “dwell” for an extended time. In this study 90% of the infections were treated successfully. So far only open trials have been done in tunnelled catheter-related bacteremia, with or without additional parenteral antibiotic therapy. With antibiotic-lock more catheters were salvaged. For instance vancomycin has been used in a dosage of 1-5 mg/mL mixed with 50-100U of heparin and 2-5 mls are instilled into the catheter to “dwell” for 12 hours\(^{24,25}\). The duration of treatment has varied, but it is most often 2 weeks\(^{24,26}\). Up to date no RCT’s have been performed in patients with cancer. Therefore future trials are needed and antibiotic lock therapy should not be common practice as yet.

A further aspect in preventing infections in oncology patients was reviewed in Chapter 6. In this chapter a systematic review is presented to assess the evidence for the effectiveness of selective gut decontamination (SDD) to decrease bacteremia and infection-related mortality during neutropenic episodes in oncology patients. Medline, Embase and the Cochrane Library issue 2, 2002 were searched. The main outcome was the number of patients with documented bacteremia’s (Gram-negative or Gram-positive bacteremia) and infection related mortality. A total of 21 studies met the inclusion criteria. The incidence of Gram-negative bacteremia’s significantly decreased and showed an OR of 0.39 (95% CI 0.24-0.63). Infection related mortality due to bacterial causes decreased with the use of SDD, an OR of 0.49 was seen (95% CI 0.27-0.88). In conclusion this systematic review has shown that TMP/SMZ or quinolone based SDD regimen started before the onset of neutropenia reduces Gram-negative bacteremia and infection related mortality in neutropenic oncology patients. From our results we highly recommend the use of TMP/SMZ or quinolone prophylaxis to cancer patients with a high baseline risk for infections, such as patients with hematological malignancies, autologous and allogenic bone-
marrow transplant patients and solid tumour patients who have an expected neutropenia of at least 7 days.

A similar debate has been held in the ICU as to whether or not antibiotic prophylaxis should be used to prevent or decrease respiratory tract infections. Although the endpoints in ICU patients are different, namely respiratory tract infections and the method of SDD in these patients differs from oncology patients, also in this ICU group the lack of a standard protocol and insufficient numbers have made it difficult to derive meaningful conclusions from individual clinical trials. Recently a well designed randomised controlled trial was performed in an ICU setting with the inclusion of 934 patients, assessing the effect on ICU mortality, hospital mortality and the acquisition of resistant bacteria. The SDD given was polymyxin E, tobramycin, and amphotericin B combined with a 4 day course of intravenous cefotaxime. In the SDD group 15% of patients died in ICU versus 23% in the control group. Resistant Gram-negative or Gram-positive organisms were found in 16% of the SDD patients and in 26% of the control patients. Their conclusion is, SDD can decrease ICU and hospital mortality and colonization with resistant Gram-negative aerobic bacteria in a setting with low prevalence of vancomycin-resistant enterococcus and methicillin-resistant Staph. aureus. At the same time a Cochrane review was published addressing the same question. In the 16 included trials that tested a combination of topical and systemic antibiotics, there was a significant reduction of both respiratory tract infections (OR 0.35 CI 0.29-0.41) and total mortality (OR 0.80 CI 0.69-0.93). The design of the review did not allow conclusions to be drawn on resistance data. However, the data of this systematic review and the large RCT provide evidence that this strategy should be implemented in clinical ICU practice.

To improve our understanding of other supportive care issues systematic reviews on the research performed are useful. A problematic aspect in pediatric oncology even in multi-centre trials is the number of patients involved in the trial. Because the size of the group is small it is often difficult to detect a significant difference in the effects of two therapies given. Therefore systematic reviews should be considered essential tools for researchers and health-care workers. Systematic reviews allow a more objective appraisal of the available evidence and contribute to resolve uncertainty when original research, reviews and editorials disagree. Meta-analysis, if possible, reflects a weighted average of the results in which larger trials have more effect than smaller trials. If there is no heterogeneity between the included studies an overall effect can be presented with a confidence interval. Systematic reviews can then contribute to considerations regarding the applicability of the study results. Systematic reviews are also important to define areas in which further trials are warranted. The quality of these reviews will only improve if groups collaborate as is advocated in the Cochrane Collaboration Method group. Until now pediatric oncology was reviewed by the Cochrane Orphan group, but fortunately as from 2004 pediatric oncology will have its own Cochrane Childhood Cancer Review group (Dr. L.C.M. Kremer, EKZ/AMC Amsterdam, in collaboration with the Dutch Cochrane Center).
In chapter 7 we presented a prospective study on vaccinating IgG-negative children with cancer in an early stage of their disease with the live-attenuated VZV vaccine. We achieved 72.7% seroconversion after the first dose. This is the first cohort of pediatric patients with cancer who received the VZV vaccine without interrupting the chemotherapy and the first cohort where the vaccine is introduced in a relative early phase of the chemotherapy. This study demonstrates that it is possible to administer this live attenuated vaccine during chemotherapy. Although the seroconversion is somewhat lower than in the study of LaRussa et al 30 who vaccinated 509 leukemic children in the maintenance phase, with suspension of the chemotherapy, our study is promising in decreasing the incidence of varicella zoster infection during chemotherapy treatment and most important decreasing complications due to varicella zoster infection.

One option to decrease varicella infection is to immunize all children, as part of a routine vaccination programme. This is now done in the USA. In the USA varicella vaccine has been licensed since 1995. Vaccine coverage assessed by the 2000 National Immunization survey in the USA was 68%. In order to achieve disease control vaccination coverage of over 90% is needed 31. It has been proven that the incidence of admissions for varicella and complications thereof have decreased significantly since the introduction of the routine varicella immunization programme. The future lies in total prevention of varicella by achieving an adequate vaccination coverage. Before this coverage has been achieved it is extremely important to recognize the “at high risk” patient (immuno compromised patients and pregnant women) who are at even higher risk of complications because of the relative low herd immunity 32. Furthermore other countries do not find vaccinating all children to be cost-effective. The risk of complications in “normal” children is so low, that this does not warrant routine immunization. Thus in both these groups it will be of extreme importance to offer seronegative immunocompromised patients varicella protection as soon as possible after diagnosis.

Our cohort of patients will be extended obtaining more data on time to seroconversion, adverse effects and seroconversion after a second dose of vaccine.

In patients acquiring varicella infection or herpes zoster infection oral treatment has improved. It is known that aciclovir has poor oral bioavailability and therefore should be dosed at least 5x per day. Newer drugs are available, valaciclovir and famciclovir. These drugs are rapidly converted to aciclovir and the bioavailability is 3-5x higher than that of oral aciclovir in humans 33. This results in improved benefit, and most likely improved compliance. These drugs are not registered for pediatric use yet. Future trials should focus on the efficacy of these newer drugs in immunocompromised children.

**Overall conclusion**

Many aspects of preventing and predicting infections in pediatric oncology patients have been addressed in this thesis. Proposals for future trials have been presented. The results of future
prospective trials and the evidence acquired from systematic reviews, will allow the best available treatment of infectious complications to be applied to our pediatric oncology patients.

Reference List


