Large single center studies have been reporting their results on surgical, urological and oncological aspects of surgical treatment for prostate cancer. Single surgeon results have only been presented scarcely and then mostly reflect high quality and probably not the standard quality achieved in all centers.

The intersurgeon variability of surgical skill can be translated not only in peri- or postoperative complications but also in statistically significant differences as concerned to PSA progression.

Therefore it is clear that the surgeon who performs radical prostatectomy matters. The surgeon must inform his patients about his own outcomes and not about the results of high standard centers that have reported their experience. Indeed, there can be a relevant difference in morbidity and cancer cure.

92

MLL gene rearranged leukemia: from biology to therapy

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Childhood MLL gene rearranged acute lymphoblastic leukaemia (abbreviated as MLL) is characterised by a high incidence of a high white blood cell count, organomegaly, central nervous system involvement, myeloid features and the very immature CD10 negative precursor B-lineage phenotype. In vitro and in vivo mouse models showed that MLL grow better on stromal cell layers and are more resistant to cell death due to serum deprivation than other types of ALL. Most often MLL gene abnormalities reflect translocations; most frequent is the t(4;11) followed by t(11;19, t(9;11) and many other rare translocations. There are some data to suggest that > 1yr of age, the fusion partner is important for outcome: t(9;11) and t(4;11) do worse than others. The incidence of MLL is very high below 1 year of age (80%), and low in older children and at adult age the incidence is slightly increasing again. MLL has a relatively poor outcome with an EFS of 40% or less. Children > 1yr with MLL do better than infants < 1yr with MLL. Relapses occur relatively early; * occur within 1 year of diagnosis. This implies the need for intensive chemotherapy applied early. The benefit of allogenic stem cell transplantation in MLL is questionable and in a recent (not randomised) meta-analysis of MLL, survival in the transplanted t(4;11) group, especially those with an unrelated donor was not better than in the t(4;11) group receiving chemotherapy only. MLL shows a relative resistance in vitro and in vivo to glucocorticoids and L-asparaginase. However, MLL is in vitro significantly more sensitive to ara C and 2CdA than other types of ALL and AML, which can partly be due to a high expression of the nucleoside membrane transporter ENT1. Also clinical studies suggest that MLL benefits from treatment with HD-araC. Based upon these data, a large international collaborative treatment protocol (Interfant) has been designed that started in 1999. For future perspectives it is important that gene expression array analyses by independent groups have shown that MLL is characterised by a unique genetic profile, different from other genetic subtypes of ALL and AML. Of importance is also that by this genetic fingerprint genes may be identified that play a role in the leukemogenesis of MLL and that may serve as new therapeutic targets. Flt-3 is an example of this. Different studies showed that (wild type) flt-3 is significantly overexposed in MLL compared to other ALL and AML. In addition, inhibitors of flt-3 were shown to have specific activity in MLL cell lines, in a mouse model transfected with MLL and in patient samples from MLL cases, all these data compared to non-MLL ALL. This offers the opportunity to study flt-3 inhibitors in MLL.

93

Risk adapted treatment for childhood ALL: the BFM experience

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Close to 80% of pediatric patients with acute lymphoblastic leukemia (ALL) can be cured. To reduce the rate of relapses, but also to limit treatment morbidity, risk-adaption of treatment has been developed on the basis of extensive risk factor analysis. In addition to clinical factors (e.g. age, WBC), the immunphenotype and cytogenetic results, the early in vivo treatment response as determined by cytology had evolved as the most important predictor for relapse. Recently, the International BFM-Study-Group has demonstrated that standardized detection of MRD by identifying clone-specific T-cell receptor- (TCR) or immunglobuline (Ig) gene rearrangements can provide new, highly specific prognostic information. This allows to define three risk groups if BFM chemotherapy is being used (van Dongen et al., LANCET 352: 1731-38; 1998). Standard risk (SR): no evidence of MRD using two highly sensitive markers (sensitivity <=10-4) on day 33, and in week 12 before consolidation; medium risk (MR): MRD positive at d33 but low-positive (=10-3 at w12. For the new trial ALL-BFM 2000 refined logistics were developed to guarantee on-time MRD results. At least two independent Ig/TCR gene rearrangements had to be identified as PCR targets individually from the diagnostic material (bone marrow, BM). The two follow-up samples from week 5 and 12 (also BM) were analyzed quantitatively by real-time PCR (LightCycler). MRD results were reported to the participating hospitals via the study center 4-6 weeks later, after cross-checking with additional patient data relevant for stratification. More than 1200 eligible patients were enrolled since the start of the new trial. MRD-based stratification was possible in 81%. Based only on MRD results, 41% of the patients were eligible for SR, 50% for MR, and 9% for HR. When the additional risk group definitions (prednisone response, induction failure, translocation t9;22, or t4;11) were included according to protocol, all eligible patients could be stratified: SR comprised 33%, MR 52%, and HR 15% of the patients. In a randomized study with the AIEOP ALL group, postinduction treatment is reduced for SR, modified for MR, and intensified for HR patients. MRD-based stratification is feasible in a multicenter trial for childhood ALL if reliable logistics and lab methodology are available. Trial ALL-BFM 2000 is investigating whether this effort can be converted into a therapeutic benefit.

94

Prognostic relevance of minimal residual disease in risk stratification of childhood ALL.

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The study of Minimal residual disease (MRD) as "surrogate" marker of molecular response to treatment, has drawn great interest because of the potential of tailoring treatment and the possibility of gaining insight into the nature of a cure. PCR-based MRD detection by Immunoglobulin (*Ig*) and T-cell receptor (*TCR*) gene rearrangements can be applied in more than 90% to 95% of childhood Acute Lymphoblastic Leukaemia (ALL) cases. Accordingly, several retrospective studies of MRD in childhood ALL have used one of the different PCR approaches for the detection of antigen-receptor gene rearrangements. The promising results on the predictivity of MRD evaluation at the end of induction treatment has challenged the need of a new definition of remission. Until now, most PCR-based MRD studies used semiquantitative methods for the detection of *Ig* and *TCR* gene rearrangements The introduction of Real-time Quantitative PCR (RQ-PCR) has resulted in the improvement of sensitivity, specificity and better quality control of the MRD data. Highly sensitive PCR techniques (detection limit $1x<10^{-4}$) allow the identification of a significant proportion of ALL cases with excellent clinical outcomes in the presence of negative MRD findings at early time points in treatment. By contrast, patients with 10^{-2} or more leukaemia cells during any phase of remission induction should be regarded as having a very high risk of relapse, thus becoming eligible for early transplantation or experimental treatment. How to use "intermediate" range of positive MRD findings ($>1x10^{-4}$ but $<1x10^{-2}$) is still unclear. Such patients might benefit from further intensification, but that possibility needs to be substantiated by randomised clinical studies. Thus, the German-Austrian BFM and Italian AIEOP study groups have adopted a MRD-based risk group classification for treatment stratification in their ongoing clinical studies. It is hoped that a more sensitive and specific evaluation of remission and early response to treatment could speed further improvement in cure rates for children with ALL.

95

What is the best treatment for ALL in adolescents and young adults?

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It is well known that adolescents with acute lymphoblastic leukemia (ALL) have a worse outcome compared to children 1-9 years of age. In a series of papers presenting results from recent pediatric ALL trials, event-free survival (EFS) ranged from 74-87% for children 1-9 and 55-70% for children > 10 years of age. The incidence of T-cell ALL is twice as high in adolescents compared to younger children. Restricting the analysis to patients with B-precursor ALL, patients >10 years of age have an increased incidence of common ALL antigen negativity, hemoglobin >11 grams, Philadelphia

chromosome positivity, and a lower incidence of enlarged lymph nodes or liver. Patients >10 years of age have a 10-15% risk for avascular necrosis of bone and the risk increases with age at diagnosis. Leukemic cells from patients with B-precursor ALL show increased in-vitro drug resistance to prednisone and daunorubicin compared to cells from younger patients.

Two recent studies have shown that adolescents treated on pediatric leukemia trials have a better EFS than similar adolescents treated on adult leukemia trials. EFS on the pediatric trials was approximately 65% at 5 years compared to 40% for adult trials. The reasons for the large EFS differences are not readily apparent. Treatment protocol, actual drug intensity, compliance with therapy, and supportive care practices should be evaluated in an effort to explain the EFS differences.

In the most recent Children's Cancer Group (CCG) ALL Protocol 1961, adolescents >10 years of age received a four-drug induction with vincristine, prednisone, L-asparaginase, and daunomycin. A Day 7 bone marrow was performed: patients with ≤ 25% blasts were considered rapid early responders, while patients with >25% blasts were considered slow responders. Rapid early responders were randomized to standard or increased treatment intensity during consolidation, interim maintenance (IM), and delayed intensification phases (DI), and to receive one or two IM/DI combinations. Slow early responders received increased treatment intensity and 2 IM/DI phases (augmented BFM). The four-year EFS for patients 16-21 years of age (N=253) is 72.5%. A new protocol is being developed by the Children's Oncology Group (COG), which will accrue patient up to 30 years of age. A number of adult cooperative groups have shown interest in participating.

96

Childhood ALL: from the randomized clinical trials to an evidence-based approach.

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Childhood ALL is a relatively rare disease in which a remarkable progress has been achieved in the last three decades, with approximately a 75% Event Free Survival at 5 years from diagnosis.

The randomized clinical trials (RCTs) have been one of the major factors responsible of the therapeutic progress in the last 20 years. The strategy of RCTs became more complex due to the modest improvement that can be expected in outcome. Problems to be considered are: number of patients, selection of appropriate questions, time to get final results. Large international cooperation has become a crucial requirement.

We describe the experience in RCTs of I-BFM-SG (International BFM Study Group) created by H. Riehm in 1986.

A. 1989-1991: Intermediate Risk ALL: use of the same backbone protocol with different randomizations in different countries (Germany and Austria, Italy, The Netherlands, EORTC – centers from Belgium and France).

B. 1995: large international cooperation applying prospective meta-analysis to evaluate the VCR-Dexamethasone pulses in maintenance (Germany and Austria, Italy, Argentina, Chile, Hungary, Czech Republic).

C. For the first time use of the same protocol in some European countries (Germany, Austria, Switzerland, Italy) to evaluate the impact of Minimal Residual Disease (MRD) and 4 randomized questions.

D. Large international cooperation (Czech Republic, Chile, Uruguay, Argentina, Croatia, Poland, Hong Kong, Hungary, Israel) asking the same questions as in C. without MRD stratification.

A contribution to a better selection of the more relevant questions to be included in RCTs is the use of the so-called "retrospectoscope" (JCO 1997; 15: 1289-90) the critical evaluation of the information available in the literature from RCTs as well as from observational studies.

One example is presented: the TIT vs MTX alone for CNS preventive therapy has been introduced in 1971. In 2003 only, after a RCT performed by CCG, a clear conclusion has been obtained.