TREATMENT OF SLE IN CHILDREN AND ADOLESCENTS IN 2003: IS IT BETTER TO HAVE LEUKEMIA THAN SLE?

It has been interesting, if disconcerting, to have pediatric hematology-oncology colleagues recently express their sympathy for the burdens of caring for children with rheumatic disease, especially systemic lupus erythematosus (SLE). Was it just 20 years ago that the child with leukemia would keep pediatric faculty, residents, and staff in the USA very busy with the children often living only 2-3 years after diagnosis? The survival rate for acute lymphoblastic leukemia in many countries now approaches 75-80% and these surviving children are often well with only occasional minor sequelae. Our hematology-oncology colleagues comment that at least they find out whether their patients will live or die within the first five years after diagnosis.

In many countries, rheumatologists have noted an impressive improvement of five and ten-year survival rates in patients with SLE. The reasons for these short-term improvements are no doubt many: Earlier diagnosis, more aggressive treatment, better support, dialysis and transplantation. Yet recently some rheumatologists have spoken out that we should be less satisfied about how SLE patients do and especially with their long-term mortality and morbidity. Michelle Petri of John Hopkins has repeatedly suggested at various symposia (e.g., PRES meeting Utrecht, 2001, APLAR meeting, Bangkok, 2002) that we are still using an inadequate, toxic treatment program for SLE: too much oral corticosteroid side effects such as osteoporosis, hypertension, cataracts, coronary artery disease, avascular necrosis, and not enough effectiveness in preventing flares and long term organ damage. Ravelli et al. and Brunner et al. have documented significant organ damage in pediatric SLE patients with our current treatment regimens and suggest the need for early introduction of immunosuppressive agents and the toxicity of long-term steroid treatment. (1-2)

In 13 years at La Rabida/University of Chicago, SLE and MCTD have been the most difficult adolescent patients to manage, particularly when they have severe glomerulonephritis. No doubt treatments and outcomes vary with pediatric SLE in different pediatric rheumatology centers around the world, but there are also likely to be many similarities. Organ damage gradually increases with time in some patients, even with pulse methylprednisolone,

cyclophosphamide, azathioprine, and other immunosuppressive therapy.

In some families cultural or alternative medicine issues may prevent or limit use of the corticosteroids, cyclophosphamide, and others of our standard drugs. In teens compliance may be a major problem and in some teens and families "patient fatigue" occurs where the patient and family lose faith and become more and more hopeless. Medicine compliance, clinic attendance, and patient follow-through drop significantly. End stage renal disease often eventually results over 5-15 years even with aggressive treatment. The same patients who are problem patients before dialysis and transplant may have even more difficulties after renal failure, sometimes leading to mortality after much suffering. There is absolutely no doubt that the treatment of juvenile SLE has much room for improvement.

In his Commentary in this issue of PROJ, Lehman outlines the argument for an aggressive use of pulse cyclophosphamide in 2003 for children with SLE, both renal and extra-renal. He identifies three important issues that must be addressed in many of our patients. He points out that our first responsibility is to select out the high-risk patient. This challenge remains daunting. There are several risk factors that have been published such as ethnic group and Class IV DPGN on renal biopsy (3-7). At present, there is no reliable way at disease onset to select out the children and teens that will do poorly. As noted by McCurdy et al. in 1992, there are several factors mid-course that select our high-risk patients who are likely to progress to renal failure. These factors include persistent hypertension and abnormal urinalyses, anemia, and an elevated creatinine.(7) This inability to pick out at-risk patients very early in the disease course before organ damage occurs remains a major obstacle to improving the 10-20 year outcome of our patients.

Other factors that may play a role in poor outcomes include inadequate compliance and "patient fatigue". Lehman would add persistent hypo-complementemia on less than 0.5 mg/kg/day of prednisone as another indication for IV cyclophosphamide. This latter recommendation requires more study and but his point is on target. It is crucial that to suppress the lupus renal disease in an early stage and not let it gain momentum. Early use of cyclophosphamide may also minimize corticosteroid toxicity, ensure better compliance, and decrease the risk of progression to renal failure and death due to "patient fatigue". It is also likely that genetics plays a major role in some patients who develop severe SLE problems. Future clinical availability of genetic risk factors may help us select out these high risk patients and treat them more aggressively from the time of diagnosis.

Lehman's second issue is how much cyclophosphamide to give to each patient. Lehman is a proponent of high dose, monthly pulse cyclophosphamide (700-1000 mg/m2) up to a maximum of 20 grams with the classic NIH protocol. Results in his own series of patients at Hospital of Special Surgery in New York demonstrate that the regimen can work.. (8) There are risks of significant toxicity such as infertility and malignancy, but these risks appear to be less than often feared by many parents and physicians. The risk of infertility appears acceptable as a maximum of 1/6 appear to develop infertility after cyclophosphamide treatment for malignant conditions. Lehman correctly notes that infertility also may be a major problem once on high dose chronic corticosteroid therapy, with chronic severe inflammatory disease, not to mention dialysis, transplant, and life-threatening disease. Fortunately, no significantly increased incidence of malignancy has yet been attributed to the routine cyclo-phosphamide therapy for lupus in children, though we still worry.

Lehman suggests that giving lower doses of cyclophosphamide or giving it for shorter periods of time invites treatment failure. The fact is the question of whether the monthly dose of cyclophosphamide can be varied for any individual patient cannot be conclusively answered, as there is no evidence-based data in children. The usual standard NIH practice of pushing the dose until the nadir white blood cell count is 3000-4000 cells/mm3 has not compared to more or less vigorous approaches in children. Yet it is clear that the use of cyclophos-phamide emphasized by Lehman is frequently efficacious and there are no studies yet documenting that a different approach with more or less intravenous cyclophosphamide is as effective or less toxic. At present, this treatment regimen remains the only regimen supported by evidence-based medicine.

It is also not known if mycophenolate or azathioprine can be used for each patient with severe SLE renal disease in children with the same results. The comparative studies have not been done in children and teens. In the meantime, some pediatric rheumatologists may still prefer these other immunosuppressive drugs to cyclophosphamide. There are only short-term studies of these drugs in childhood SLE nephritis. (9,10) In some countries cost may make these drugs attractive. Yet while these immunosuppressives may be appropriate for certain low risk SLE patients, the evidence is not yet there to support the use of these other drugs for high-risk patients. The hooker is that, as discussed above, there is no reliable way at diagnosis or in the first year of the illness to be sure who will be a high-risk patient and who won't. This uncertainly makes the decision whether to use

cyclophosphamide versus azathioprine or mycophenolate in children and teens risky. Data from adults with these oral medications is not necessarily easily transferable to childhood SLE. In that situation the safer and wiser course at this time may be that when in doubt, be aggressive with the use of intravenous cyclophosphamide.

Lehman lastly addresses what to do for the patient who fails standard cyclophosphamide therapy. It is also important to include the issue of what to do with the child or teen with high-risk renal disease who cannot tolerate intravenous cyclophosphamide. Again there is limited evidence-based medicine. Lehman has experience with the combination of monthly intravenous cyclophosphamide and methotrexate with good results. Other options include combinations of oral immunosuppressives such as cyclophosphamide, azathioprine, mycophenolate, and/or cyclosporine A. Biologics such as anti-CD20 may eventually have an adjunctive role. Experimental measures such as stem cell transplant and high dose cyclophosphamide without transplant must be studied more but should be considered now on a case-by-case basis under research protocols.

In the treatment of severe SLE in children and teens in 2003, there are many more questions than answers. In this issue, Lehman lays out cogently the argument for the aggressive use of intravenous cyclophosphamide to decrease mortality and morbidity. This experience should be the starting point of treatment for most of the severely involved children with lupus and should be used without hesitation. It is hoped that early use of cyclophosphamide will lessen or prevent the compliance and patient fatigue problems. Yet in different patient populations with lower risk children, other drugs may be effective. To determine what to use when, international, multicenter studies are needed where different immunosuppressive and biological regimens can be compared utilizing risk factors as oncologists use histological markers.

Our subspecialty has been handicapped by insufficient statistical power to perform good clinical studies on SLE treatments at any one center. International studies may be soon possible with an n in the hundreds if not thousands (Note: The Asian-Pacific region has approximately 1 billion children). As Ravelli and Martini note in an accompanying editorial in this issue, the world of pediatric rheumatology is shrinking rapidly and in-depth international cooperation is now not only feasible and desirable, but also crucial to our development as a subspecialty and the welfare of the children we care for. Time to get to it.

Charles H. Spencer, MD

University of Chicago/La Rabida Children's Hospital

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