Testicular Relapse in Acute Lymphoblastic Leukemia (ALL): Guidelines Must be Changed

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Introduction

The testis is the second most frequent site for extramedullary recurrence in ALL. Local therapy is not uniform in different study groups.

In the classical Protocol POG 8034, as well as in ALL-REZ, COG, BFM 2002, UK ALL-R3 or the COPRALL, there is no clear specific reference to unilateral or bilateral testicular recurrence. But it appears that everyone accepts that recurrence in the testicular sanctuary will always, at least potentially, be bilateral (even if it may be only more evident on one side) and then requires local irradiation, classically with 24 Grays. Because it entails complete loss of hormonal function and testicular atrophy (with concomitant sterility), BFM relapse strategies believe that the strategy offers the chance of spontaneous puberty without hormonal substitution, at least, in a reasonable number of patients. These are the guidelines that I believe really need revision, so that, at least many patients (and not only a reasonable but non defined number) remain fertile and not hormonally dependent [1-5].

Mini Review

A 7-month-old male with ALL-B Calla negative, was seen on the 2nd January 2002 and treated according to Protocol POG 8034. One year later (October 2003) he had a successful Bone Marrow Transplant. Nevertheless, when aged 5 years he showed a large recurrence in the left testicle (confirmed by FNAC), which rapidly reached the size of a hen’s egg, albeit with an apparently clinically normal right testis. Peripheral Blood and Bone Marrow where normal and 2 FNACs on the Right Testicle proved also to be completely normal. If one irradiates both testicles, even when only one appears clinically normal, 2 FNAC’s were negative and also because the testicle, due its location, could be easily evaluated through frequent and simple palpation, even by the Parents[5,6].

At this stage I was asked to do a bilateral orchydectomy, as the POG Protocol justify routine Castration (surgical or radiotherapeutic) and, if so, on what grounds does it base its recommendations?

Taking into question his future quality of life, I considered that, if the child was going to survive (as fortunately happened), he should still have a functioning testicle, not only under an hormonal point of view but also in what concerns fertility (even if admiting possible damage from BMT and Chemotherapy (with Vincristin, Doxorubicin and Prednisolone), as experience has shown that, around half of those with ALL will be infertile (although children having a better prognosis than adults).

So, I only performed a Left Orchyepididymectomy, leaving the Right Testicle alone (the left spermatic cord proved to be free of disease involvement ).

I believe that Guidelines are extremely valuable but certainly not always the final word. Each Patient is a Patient, and I agree that “Guidelines are not God’s Lines”, each one having to question and understand what he thinks is best for the Patient.

I still remember that, when the results of Rosen’s Osteosarcoma Patients (at the Memorial Hospital, in New York) were reviewed, a significant number of them had had alterations to the Classical Rosen T10 [6,7].

If one irradiates both testicles, even when only one appears clinically and histologically involved (what is not so common), one can never prove whether that testicle was really normal or, eventually, minimally involved. So, the question to be asked upfront, is how can the POG Protocol justify routine Castration (surgical or radiotherapeutic) and, if so, on what grounds does it base its recommendations?

Even the softer attitude (1200 or 1500 instead of 2600 Grays) proposed by the BFM, looks to me unacceptable, because that strategy only seems to offer a chance for spontaneous puberty without hormonal substitution on a “non defined” substantial part of patients. Also nothing is known about eventual congenital malformations brought about by those “irradiated” spermatozoa. Also numbers of
isolated testicular relapses are statistically very small and many years will have to pass for any acceptable conclusion. So, I believe one has, nowadays, only to rely on bibliography, reasoning and common sense!

It is known that, in a few patients that have had a laparotomy at the time of testicular relapse, most had leukemic infiltration of the abdominal lymph nodes, liver and spleen. Also, treatment by irradiation of the remaining testicle, in an apparently isolated an usually late, testicular relapse, is frequently followed by a bone marrow relapse some time later. If the leukemia recurs it is almost certainly because the overall disease has not been controlled by the transplant or the chemotherapy given, and certainly not because of the preserved testicle, above all, so easily controlled by palpation.

So why to be so dogmatic about the need to destroy a clinically and histologically normal testicle? If there is the slightest doubt about a recurrence (testicular enlargement, that even the Parents can perform frequently), then an orchidectomy can be rapidly performed. But even if that would happen as an isolated recurrence, the likelihood of spreading from that sanctuary to the whole body, is certainly minimal. And, obviously, neither chemotherapy or bone marrow transplantation would be excluded, if indicated [8-10].

Further, if the preserved contralateral testicle is still present, any of its alterations is most likely an early sign of further generalized recurrence. Certainly an earlier and easier way to detect a recurrence than from marrow aspirates or blood sampling). Thus entailing further salvage chemotherapy or transplant.

Unfortunately my advice was not followed and the testicle that I had refused to remove, was “treated” with irradiation (24 Grays), thus nullifying my hopes of a more conservative approach and for a better future quality of life for that Patient.

Since then the child had no further treatment, but now 12 years later the left sided orchepididymectomy and right sided testicular irradiation. He is, needlessly and permanently under hormonal treatment has a small penis and a stunted growth. And he will never be a true father.

I believe that that this Patient was a real prof of the need to reevaluate the current guidelines for ALL. Also a Dutch Study, using only chemotherapy, showed that 5 patients, in whom irradiation of the contralateral testicle was avoided remained disease free.

When this problem was presented at a IPSO Meeting, almost all Pediatric Surgeons present, agreed on a conservative approach, the only exception being a Pediatric Oncologist, quoting the "sacred" POG 8304.

So I firmly believe that POG 8034 (and other Protocols for AAL, that unfortunately maintain the same “classical” philosophy), need to be reviewed, so that common sense and future quality of life for the Patients will prevail, at a minimal health risk.

And now some final remarks: now, that everyone is worried with costs apart from being sterile, the treatment costs of this male patient with “Growth Hormone” and “Testosterone”, would amount to an expense of around 100 dollars per month. With a life expectancy of more 60 years (accepting a lowering dose over the years), it will mean an avoidable cost of, at least, many thousands of dollars [11,12].

References
1. NHII ALL-REZ BFM (Multicentric Study for Children with relapsed ALL).
2. Cancer Research UK UL ALL R3 Phase 3 study 2006/2013.
3. Buchanan GR, Boyett JM, Pollock BH, Smith SD, Yanofsky RA, et al. (1991) Improved treatment results in boys with overt testicular relapse during or shortly after initial therapy for acute lymphoblastic leukemia. A Pediatric Oncology Group study. Cancer 68: 48-55.
4. Castillo LA, Craft AW, Kernahan J, Evans RG, Aynsley-Green A (1990) Gonadal function after 12-Gy testicular irradiation in childhood acute lymphoblastic leukemia. Pediatric Blood & Cancer 18: 185-189.
5. Grundy RG, Leiper A, Stanhope R, Chessells J (1997) Survival and endocrine outcome after testicular relapse in acute lymphoblastic leukemia. Archives of disease in childhood 76: 190-196.
6. Kulkarni KP, Marwaha RK, Trehan A, Bansal D (2010) “Testicular relapse in childhood acute lymphoblastic leukemia: the challenges and lessons.” Indian Indian J Cancer 47: 134-138.
7. Locatelli F, Schrapp M, Bernardo ME, Rutella S (2012) How I treat relapsed childhood acute lymphoblastic leukemia. Blood 120: 2807-2816.
8. Nesbit ME Jr, Robinson LL, Ortega JA, Sather HN, Donaldson M, et al. (1980) “Testicular relapse in childhood acute lymphoblastic leukemia: association with pretreatment patient characteristics and treatment. A report for Childrens Cancer Study Group.” Cancer 45: 2009-2016.
9. Van Schewick C, Vakhonina L, Henze G, Burkhartd B, Reiter A, et al. (2008) Other extramedullary localizations in relapse of childhood lymphoblastic leukemia (abstract) Pediat Blood Cancer.
10. Von Stackelberg A, Tabien U, Van Schewick C, Schrapp M, Escherich G, et al. (2008) Bilateral involvement is an important prognostic factor in isolated testicular relapse of childhood ALL. Pediatric Blood Cancer pp: 28.
11. Wofford MM, Smith SD, Shuster JJ, Johnson W, Buchanan GR, et al. (1992) Treatment of occult or late overt testicular relapse in children with acute lymphoblastic leukemia: a Pediatric Oncology Group study. Journal of Clinical Oncology 10: 624-630.
12. Wolfrum C, Hartmann R, Brühmüller S, Fengler R, Reiter A, et al. (1997) Similar Outcome in Boys with Isolated and Combined Testicular Acute Lymphoblastic Leukemia Relapse After Stratified BFM Salvage Therapy. Acute Leukemias VI. Springer, Berlin, Heidelberg pp: 647-651.