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

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Abstract

Guidelines for the treatment of testicular recurrences need to be changed: a patient with unilateral testicular recurrence of ALL has been unnecessarily castrated by irradiation. The patient has been free of disease for 12 years, having had chemotherapy, several bone marrow transplants and left Orchypididectomy. Nevertheless, due to irradiation of the right testicle, he has been left permanently under hormonal replacement and with unavoidable infertility. This outcome could have been avoided if treatment guidelines had been changed and a different approach was taken. This confirms some more recent studies, although with the drawback of the number of affected patients being small.

Keywords: Recurrent ALL; Testicular relapse; Testicular preservation

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 have recommended to remove a clinically involved testis and to irradiate a contralateral clinically and bioptically negative testis with 15 Grays. Because it entails complete loss of hormonal function and testicular atrophy (with concomitant sterility), BFM relapse strategies have recommended to remove a clinically involved testis and to irradiate a contralateral clinically and bioptically negative testis with 15 Grays. They 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 most 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 FNAC’s on the Rigth Testicle proved also to be completely normal.

At this stage I was asked to do a bilateral orchydectomy, as the POG 8034 advised. But I refused to do it, not only because the right testicle was 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].

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 admitting 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 prognoses than adults).

So, I only performed a Left Orchypididectomy, 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 orchectomy 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 contratleral 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 and has a normal 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 contratleral 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 a 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. NHI ALL-REZ BFM (Multicentric Study for Children with relapsed ALL).