Testicular relapse in Acute Lymphoblastic Leukemia (ALL): A simple problem of common sense

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Abstract

The testis are the second most frequent site for extra medullary 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 (1,2,3, 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 or complementary orchiectomy.

Keywords: Testis, Leukemia, Lymphocytes, Histology.

Accepted on 19 March, 2021

Description

We believe that that philosophy is quite wrong, mainly considering the future wellbeing of the patients that should be given the change of a possible "normal life" survival. 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.

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. 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 radio therapeutic) and, if so, on what grounds does it base its recommendations?

Taking into question his future quality of life, I considered that, if a child is going to survive, 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, as experience has shown that, around half of those with ALL will be infertile (although children having a better prognoses than adults).So we believe that one should take a conservative attitude, if recurrence appears only on one side and provided FNAC is negative on that, so-called, still "normal" testicle and also because, due its location, the testicle can be easily evaluated through frequent and simple palpation, even by the Parents [1-6].

Also nothing is known about eventual congenital malformations brought about by those "irradiated" spermatozoa. Also numbers of isolated testicular relapses are very small and many years will have to pass for any statistically acceptable conclusion. So, we believe anyone can, nowadays, to rely on bibliography, reasoning and, above all, 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 (and 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 [7,8].

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 detect), then an orchiectomy 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 nor bone marrow transplantation would be excluded, if indicated. Further, if the preserved contralateral testicle is still present, any of its alterations is most likely an early sign of further generalized recurrence, so meaning an earlier and easier way to detect a recurrence than from marrow aspirates or blood sampling).justifying further treatment [9,10].

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.

And now some final remarks: now, that everyone is worried with "costs", apart from the Patient becoming sterile, the treatment of such a 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, it will mean an avoidable cost of, at least, many thousands of dollars. Liver, kidney, immune system, and nervous system. Liver, gill and

intestine have relatively higher potential for metal accumulation than muscle [11-16]

References

1. Wen Chen, Pipei Huang, Jiaming Xu, et al. POG: Personalized Outfit Generation for Fashion Recommendation at Alibaba iFashion. Cornell University 2019.
2. G Henze, Av Stackelberg, C Eckert, et al. ALL-REZ BFM-The Consecutive Trials for Children with Relapsed Acute Lymphoblastic Leukemia. PubMed.gov. 2013.
3. Daniel Ungar 1, Toshihiko Oka, Elizabeth E Brittle, et al. Characterization of a Mammalian Golgi-Localized Protein Complex, COG, that is required for normal Golgi Morphology and Function. PubMed.gov 2002.
4. Cancer Research UK UL ALL R3 Phase 3 study 2006/2013.
5. Facile Synthesis and Anti-Mycobacterial Activity of Isoniazid, Pyrazinamide and Ciprofloxacin Derivatives Corporal punishment and Child Behavioral and Cognitive Outcomes through 5 years-of-age: Evidence from a Contemporary Urban Birth Cohort Study. PubMed.gov 2012.
6. Fumio Hayashi, Masahiro Sasa, Facile Synthesis and anti-mycobacterial activity of Isoniazid, Pyrazinamide and Ciprofloxacin Derivatives, Genetic analysis of revertants isolated from the rod-fragile fliF mutant of Salmonella. J STAGE. 2016.
7. GR Buchanan, JM Boyett, BH Pollock, et al. 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. 1991; 68(1): 48-55.
8. LA Castillo, AW Craft, J Kernahan, et al. Gonadal function after 12-Gy testicular irradiation in childhood acute lymphoblastic leukaemia. Med Pediatr Oncol. 1990; 18(3): 185-9.
9. RG Grundya, AD Leiperc, R Stanhopeb, et al. Survival and endocrine outcome after testicular relapse in acute lymphoblastic leukaemia. Arch Dis child 1997; 76(3): 190-6.
10. KP Kulkarni, RK Marwaha, A Trehan, et al. Testicular relapse in childhood acute lymphoblastic leukemia: The challenges and lessons. Indian J Cancer 2010; 47(2): 134-8.
11. Franco Locatelli , Martin Schrappe, Maria Ester Bernardo, et al. How I treat relapsed childhood acute lymphoblastic leukemia. Blood. 2012; 120(14): 2807-16.
12. ME Nesbit Jr, LL Robison, JA Ortega, et al. Testicular relapse in childhood acute lymphoblastic leukemia: Association with pretreatment patient characteristics and treatment. A report for Childrens Cancer Study Group. Cancer 1980; 45(8): 2009-16.
13. Van Schewick C, Vakhonina L, Henze G, et al. Other extramedullary localizations in Relapse of childhood lymphoblastic leukemia (abstract) Pediat Blood Cancer. 2008
14. Von Stackelberg A, Tabien U, Van Schewick C.,et al. Bilateral involvement is an important prognostic factor in isolated testicular relapse of childhood ALL. Pediatric Blood Cancer 2008 suppl:28
15. Wofford MM, Smith SD, Shuster JJ, et al. Treatment of occult or late overt testicular relapse in children with acute lymphoblastic leukemia: A Pediatric Oncology Group study. J Clin Oncol. 1992; 10(4): 624-30.
16. C Wolfromr. Hartmann S. Brühmüller, et al. Similar outcome in boys with isolated and combined testicular Acute Lymphoblastic Leukemia relapse after stratified BFM salvage therapy. Acute Leukemias VI. Springer, Berlin, Heidelberg, 1997. 647-651.

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