TRIP Biovigilance Symposium 2019

TRIP
Hemo- en biovigilantie

28 EATCB

28TH CONGRESS OF EUROPEAN ASSOCIATION OF TISSUE AND CELL BANKS
LEIDEN
THE NETHERLANDS

Workshop: Serious adverse reactions and events (case studies)

Case 1

Sjors van Kats
Responsible Person / Bone
ETB-BISLIFE

The Event

- At the Tissue bank human donated bone tissue is aseptically processed in a cleanroom (GMP Class A within Class B background)
- Technicians are trained for aseptic preparations and wear full garment and sterile gloves for working under GMP Class A conditions
- All used materials and instruments are sterile
- At final packaging the prepared bone chips are scooped into a sterile primary container that is placed directly on an ethanol-disinfected cleanroom scale
- The primary container is closed and placed in a second sterile container
- The secondary container is closed and carried out of the cleanroom via a pass-through

=Yes =No

Questions

With this procedure:

- can the outside of the secondary container be considered sterile?
- can the outside of the primary container be considered sterile?

Why is the outside of the primary container not sterile?

- Have the aseptically prepared bone chips become contaminated?
- Does this procedure carry a risk to the patient when the tissue product is used for transplantation?

What is the risk to the patient?

- Should this be reported to the competent authority?

Serious adverse event (green) or
serious adverse reaction (red)?

Handling of the Event

- Placing a sterile container on a ethanol-disinfected cleanroom scale was considered as a possible contaminating step
- The product insert claimed that the primary packaging was sterile
- During a surgery OR personnel at the operating field may touch the outside of the primary container (considering it to be sterile) and then pass possible contamination to other sterile instruments and materials on the operating field, and thereby introduce a risk of infection in the patient
- The CA was informed about this serious adverse event
- A recall was initiated of all distributed products (734) that had been produced according to this procedure; all products in stock of the Tissue bank were quarantined (235). From hospitals 85 unused products were retrieved
- No report of possible infection has ever been received from the appr. 649 transplanted units
- Swabs taken from the outside and the inside of the primary container of 30 quarantined items did not show growth of microorganism
- The final packaging procedure was revised
- All quarantined units were aseptically repackaged in new sterile containers and released for distribution

Reportable serious adverse events (non-reproductive T&C)

From: COMMON APPROACH FOR DEFINITION OF REPORTABLE SERIOUS ADVERSE EVENTS AND REACTIONS AS LAID DOWN IN THE TISSUES AND CELLS DIRECTIVE 2004/23/EC AND COMMISSION DIRECTIVE 2006/86/EC , VERSION 2.8 (2019)

The following criteria should be applied to decide which adverse events are reportable to Competent Authorities and, subsequently, to the Commission for **Non-Reproductive T&C**:

- *1) Inappropriate tissues/cells have been distributed for clinical use, even if not used;*
- *2) The event could have implications for other patients or donors because of shared practices, services, supplies or donors;*
- *3) The event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient specific) allogeneic tissues or cells;*
- *4) The event resulted in the loss of a significant quantity[3] of unmatched allogeneic tissues or cells.*

[3] A significant quantity should be understood as a quantity that has caused patient treatments to be cancelled or delayed.

STYRELSEN FOR
PATIENTSIKKERHED

Case 2 : Genetic condition in a child conceived with donor sperm

SARE workshop

12th TRIP Biovigilance Symposium 16 October 2019

28th Congress of EATCB

Danish Patient Safety Authority/Anne Cathrine Bollerup

Description of the event/reaction

- Child conceived with donor sperm born 28JUL2018 in Brazil. Newborn screening on 06AUG and 17AUG2018 showed elevated immunoreactive trypsinogen (IRT), 353 ng/ml and 372 ng/ml (ref. 110 ng/ml) respectively. Sweat test on 28AUG2018 (pilocarpine iontophoresis) was positive, 100 mmol/l, compatible with cystic fibrosis. The diagnosis has not yet been molecularly verified.

- Donor had a negative screening result in 2010 with a panel of 32 CFTR mutations (laboratory: LABCORP, USA) recommended by ACOG/ACMG (The American College of Obstetricians and Gynecologists/American College of Medical Geneticists, i.a. the scientific societies). The family history of the donor is negative for cystic fibrosis.

=Yes =No

Questions to ask the participants

- Would you report this case as a SARE to the Competent Authority?
- Report as a SAE (green) or a SAR (red)?
- Is genetic disease in a child born by help of sperm from donor (other than partner) **explicit** to be understood as a SAR according to the EU T&C Directives?
- Is genetic disease in a child born by help of sperm from donor (other than partner) acknowledged and referred to as a SAR (in the Common Approach document / V&S guideline)?
- With the negative screening result of the donor (panel of 32 CFTR mutations) is it then proved that donor is not a carrier of Cystic Fibrosis?
- Should sperm from the donor be quarantined at this moment?

Description of the event/reaction II

- The donor and donor sperm straw was in quarantine under the investigation.
- Genetic result from the child includes a full sequencing/next generation sequencing of the CFTR gene. No mutations were found.
- The Sperm Bank suggested to the mother of the sick child that she requested for an MLPA analysis (Multiplex Ligation-dependent Probe Amplification), a method that can detect deletions and duplications in the genes.
- The Sperm Bank sends a straw from the donor to their laboratory (Amplexa Genetics, Denmark) for MLPA analysis

Questions to be asked to the participants II

- With the negative screening result of the child including a full sequencing/next generation sequencing of the CFTR gene is it then proved the child has not Cystic Fibrosis?

- Can the Sperm Bank ask the mother of the sick child for the result of examinations without informed consent?

- Can the donor deny to let the Sperm Bank examine his sperm for CTRF mutations?

What consent has the donor already given for testing of his sperm?

Description of the event/reaction III

- The result of the donor's and the child's MLPA analysis arrive simultaneously.
- The child is **compound heterozygous for two deletions in the CFTR gene:** **c.(53+1_54-1)_(273+1_274-1)del** and c.(3963+1_3964-1)_(4242+1_4243-1)del
- The result of the donors test was **c.(53+1_54-1)_(273+1_274-1)del**

Questions to be asked for the participants III

- Did the child have Cystic Fibrosis?

- Was the donor a carrier of cystic fibrosis?

The outcome of the case

- The donor is a carrier of cystic fibrosis (CF), since he is heterozygous for a deletion of exons 2 and 3 in the CFTR gene
- Children of this donor have a 50% risk of having the mutation in the CTFR gene
- The donor was permanently blocked
- Letters were sent to all clinic having received donor straw
- Twelve countries were involved
- Donor was informed of his carrier status
- The Danish Competent Authority sent out a RATC (Rapid Alert Tissues and Cells) to Member States involved

Lessons to be learned

- Next generation sequencing (NGS) is not particularly suitable to detect bigger deletions which only represent a infinitesimally part of all known mutations causing disease. Today we know about totally 1639 different mutations. Therefore another method was used, MLPA, to find the mutations of the child.
- Statistically there is a very little probability to inherit this kind of deletion from both parents, as in this case.

RISK ASSESSMENT

- What is the risk for disease in a child of this donor in a Danish population, where we do not know the status of the mother?
- ANSWER: The remaining CF carrier risk in the donor given the negative screening result from 2010 is 1/240.
- The risk for an ethnic Danish mother (carrier status unknown) to have a child with CF with this donor (before we knew he was a carrier) is 1/240 x 1/25 x 1/4 = 0,004 %
- The risk for an ethnic Danish mother (carrier status unknown) to have a child with CF with this donor (when we knew he was a carrier) is 1 x 1/25 x 1/4 = 1 %

Case 3:
Autologous Peripheral Blood Stem Cells

Judith Lie, Hemovigilance and biovigilance officer
Maastricht University Medical Center+
Leiden, TRIP vigilance Symposium16-10-2019

Case 3

Female, aged 66 (AML relapse)

Day 0:

- 14:40 – 15:00 hr: reinfusion of thawed autologous PBSC units (4 bags) :

  1.2 x 10^6 CD 34 cells/kg

- 15:40 hr: hypotensive, bradycardia, sweating, O_2 desaturation (improved with 15L/min oxygen supplementation (80%))

- Treated with 2 x 1mg adrenaline, 4L saline infusion, 8 mg dexamethason, 2 mg clemastine

- ICU consulted, patient not transferred

- 20:30 hr: systolic blood pressure 110 mm Hg, pulse 100 bpm, O_2 at 10 L/min (50%), patient sleeping quietly

= Yes = No

Questions

- Adverse event (green) or adverse reaction (red)?
- Is it a serious adverse reaction?
- Are further investigations or other actions necessary?

What do you need to find out?

Facility conclusion: severe reaction to DMSO

- What is the imputability?

  Green=definite or probable Red=possible or unlikely
- Would you report this to the competent authority?

Actions taken and outcome

Actions:

- Severe adverse reaction after reinfusion of autologous peripheral blood stem cells
- Imputability: definite
- Report to TRIP and competent authority

Outcome:

Patient:

- Day +1, second reinfusion cancelled
  (4 bags, 1.8 x 10^6 CD 34 cells/kg)
- Day + 15: hematological recovery
- Day + 17: discharged from hospital

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Thank you for your participation
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