Analysis of data on breast implant associated anaplastic large cell lymphoma

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Executive summary

The increase in number of reported cases of breast implant associated anaplastic large cell lymphoma (BIA-ALCL) has become an issue of national and international concern due to the large number of women who receive breast implants each year. This report was produced in response to a request from the TGA of an updated independent analysis of Australian data on BIA-ALCL.

The TGA provided data on deidentified BIA-ALCL cases and breast implant sales data from 1992 to 2018. The data consisted of 101 cases of BIA-ALCL reported in Australia from 1983 to 2019. All BIA-ALCLs occurred in women who had textured implants. Using sales data as a denominator in the calculation of the Kaplan Meier failure function, the estimated risk of BIA-ALCL in textured implants after 10 years was 0.05%, 95%CI (0.04%-0.07%). The number needed to harm at 10 years was 2000, 95%CI (1429 to 2500), meaning that this is the estimated number of textured implants needed to be implanted for one case of BIA-ALCL to be observed after 10 years. The estimated incidence rate per 100,000 implant-years was 3.9 95%CI (3.2 to 4.8).

[redacted]

Introduction

Breast implants are used for breast augmentation and for breast reconstruction after mastectomy. According to the Australian Breast Device Registry, approximately 75% of the procedures in 2017 were for breast augmentation (1). Of those, the vast majority (97%) were bilateral procedures. Similar numbers are reported in the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database (2), were 12,277 (97%) of new breast augmentation procedures performed in 2017/18 were bilateral procedures.

Breast implant associated anaplastic large cell lymphoma (BIA-ALCL) is a rare form of non-Hodgins lymphoma. It most commonly presents with an effusion around the breast implant. The median time from insertion of implant to diagnosis of BIA-ALCL is 8 to 9 years, ranging from 2 to 32 years (3). It was first described in 1997 and since 2008, reports of BIA-ALCL have been increasing worldwide. In Australia there were 78 cases reported by 2018 compared to 49 cases by 2016. In the United States 186 cases were reported between 2012 and 2018 (4). In Netherland 43 cases were reported until 2018 (5) and in Canada there were 28 confirmed cases by April 2019 (6).

To date all the cases of BIA-ALCL have been reported in women who have been exposed to implants with textured surface as opposed to smooth surface breast implants. Breast implants can be classified according to surface roughness. In the ISO classification <10μ is considered smooth, 10-50μ is considered microtextured and > 50μ is considered macrotextured. Another proposed classification is based on a combination of manufacturing method, surface area and roughness (7).

Textured implants were designed to reduce movement of the implant and reduce the risk of capsular contraction. Polyurethane coating was added to the implants to stimulate ingrowth to the surface. In the United States and Canada most implants are smooth whereas in Australia, Europe, Asia and South America textured implants are preferred (3). In Australia according to the Australian Breast Device Registry, 75% of implants were textured, 5% were polyurethane and 20% were smooth in 2017 (1) .

Exact data on the number of women who have received breast implants are lacking, making it difficult to determine the risk of BIA-ALCL. The Australian Breast Device Registry was established in 2015, with the aim to identify health risks associated with breast devices. In lieu of available long term follow-up registry data, sales data provide yearly estimates of the number and types of breast implants supplied on the market that can be used in the calculation of incidence of BIA-ALCL. The TGA retrieved Australian sales data and undertook an analysis of the risk of BIA-ALCL in 2016. Based on sales data from 1999 to 2015 and 47 recorded cases, the rate of BIA-ALCL was estimated to be 2.3 (1.5-3.0) per 100,000 implant years, and higher for polyurethane implants than other textured implants. The estimated risk was between 1-in-1000 and 1-in-10,000 implants. The estimates were not adjusted for death or implant removal. [redacted]

Another source of denominator data is the AIHW procedure data (2). The AIHW publishes aggregated data on patient hospital episodes with procedure codes based on Australian Classification of Health Interventions (ACHI/ICD-10-AM). Yearly numbers of breast augmentation and reconstruction procedures are available from 2000 to 2017/18. The type of implants used in the procedures is not available from this source.

Due to the increase in number of reported cases, and international regulators considering taking action in relation to particular types of breast implants, the TGA considered it prudent to undertake an analysis on the data now available to determine if there is an increased risk of developing BIA-ALCL associated with a particular type of implant, or if the overall risk of developing BIA-ALCL has altered since the initial risk assessment in 2016.

The aim of the study was to determine the risk of BIA-ALCL over time and whether there is a difference in risk according to type of implant.

Methods

The study cohort consisted of women who had breast implants between 1999 and 2018 and who subsequently had the implants removed with a diagnosis of BIA-ALCL. The data were sourced from the TGA.

Data sources

The data on the cases contained information on device (manufacturer, surface), explant date, implant date and length of exposure (Appendix Table 1). Where implant dates were not recorded, it was calculated by subtracting the length of exposure from the explant date. Due to lack of exact information on surface morphology (macrotextured vs micotextured) of the implants used in many of the cases, the cases were grouped into implants with polyurethane coating ([redacted]), [redacted]

Sales data from 1999 to 2018 on number of implants sold per year were obtained by the TGA from sponsors. The sales data were classified by surface texture and manufacturer (Appendix Table 1). Expanders were excluded.

Data on breast implant procedures from the National Morbidity Database, Australian Institute of Health and Welfare (AIHW) covering the financial years from 200/01 to 2017/18 were downloaded. Number of procedures each year were extracted based on codes for breast augmentation and reconstruction with insertion of breast implants (Appendix Table 1). The proportion of procedures with textured implants were estimated based on proportion of textured implants in the sales data. To make the data comparable to the sales data the number of procedures were adjusted by counting two procedures where bilateral implants occurred.

Calculation of exposure time

Exposure time for each implant sold in a year were calculated as follows: *Exposure time = End of follow up time (1/1/2019) - Sales date (1/7/year)* using mid-period as starting point.

Implant-years for each implant sold in a year were calculated as follows: *Implant-years=No. of sales (year) x exposure time (year)*

The total number of implant-years for sold implants was calculated by summing up all implant-years.

Sales year	*No. of sales*	*Sales date*	*End follow up*	*Exposure time*	*Implant-years*
1999	8208	1/7/1999	1/1/2019	19.5 years	8208 x 19.5 years
2000	9756	1/7/2000	1/1/2019	18.5 years	9756 x 18.5 years
…	…	…	…	…	…

The procedure exposure time and procedure-years were calculated as for the sales data using the mid-period as starting date, see below:

Procedure year	*No. of procedures**	*Procedure date*	*End follow up*	*Exposure time*	*Procedure-years*
2000/01	7726	1/1/2000	1/1/2019	18 years	7726 x 18 years
2001/02	8007	1/1/2001	1/1/2019	17 years	8007 x 17 years
…	…	…	…	…	…

*estimated no. of textured procedures accounting for bilateral procedures

Time to event analysis

The Kaplan Meier method was used to estimate the risk of BIA-ALCL over time with the number of implant sales each year as denominator. The start time was the time of implant or most recent implant where there was a history of several implants. The outcome was time of explant. Censoring time for implant sales was set at 1/1/2019. The same approach was used for the procedure data. Kaplan Meier curves were calculated for textured implants, estimating overall risk of BIA-ALCL over time and risk by type of textured implants. In order to compare the risk by type of implants, a Cox Proportional Hazards model was used. The proportionality assumption was tested by including a time interaction in the model.

The incidence rates were calculated by summing up total yearly exposure time for cases divided by the sum of total yearly exposure time for sale and procedure data respectively.

All statistical analyses were performed in Stata/IC 12.1.

Results

The total number of BIA-ALCL cases reported was 101. There was one case where the breast implant occurred in 1983 ([redacted]), and in two cases information on length of exposure were missing [redacted] These cases were excluded, leaving 98 cases for analysis using sales data. Furthermore, in three cases the implant occurred in 1999 and these cases were excluded for analysis using procedure data since procedure data were not available prior to 2000.

Descriptive results

The manufacturer and surface type of the BIA-ALCL cases are presented in Table 1. Information about whether the textured surface was microtextured or macrotextured was missing in 26 of the cases. Based on the record of use of expander (n=20), most of the women had implants for cosmetic reason. The number of women who had multiple implants over time was 27 (28%). The implant and explant times are presented in Figure 1 (n=97, in one case information about implant and explant time was missing). Each implant time of a BIA-ALCL case is represented with a dot, colour coded by type of most recent implant. The right line represent time to explant. The left line represent time with prior implants in those who had multiple implants. [redacted] thereafter number of cases with polyurethane implants have been increasing.