Original article

Adjuvant taxanes and the development of breast cancer-related arm lymphoedema

M. Cariati[1,3], S. K. Bains[1], M. R. Grootendorst[1], A. Suyoi[3], A. M. Peters[5], P. Mortimer[4], P. Ellis[1,3], M. Harries[1,3], M. Van Hemelrijck[2] and A. D. Purushotham[1,3]

[1]Section of Research Oncology, and [2]School of Medicine, Cancer Epidemiology Group, Division of Cancer Studies, King's College London, [3]Directorate of Haematology and Oncology, Guy's and St Thomas' NHS Foundation Trust, and [4]Department of Clinical Sciences, St George's, University of London, London, and [5]Department of Nuclear Medicine, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK
Correspondence to: Professor A. D. Purushotham, Department of Research Oncology, King's College London, 3rd Floor Bermondsey Wing, Guy's Hospital, London SE1 9RT, UK (e-mail: ea-purushotham@kcl.ac.uk)

Background: **Despite affecting approximately one-quarter of all patients undergoing axillary lymph node dissection, the pathophysiology of breast cancer-related lymphoedema (BCRL) remains poorly understood. More extensive locoregional treatment and higher body mass index have long been identified as major risk factors. This study aimed to identify risk factors for BCRL with a specific focus on the potential impact of chemotherapy on the risk of BCRL.**

Methods: **This was a retrospective analysis of a cohort of consecutive patients with breast cancer treated at a major London regional teaching hospital between 1 January 2010 and 31 December 2012. All patients had node-positive disease and underwent axillary lymph node dissection. Data regarding tumour-, patient- and treatment-related characteristics were collected prospectively. The diagnosis of BCRL was based on both subjective and objective criteria. Multivariable Cox proportional hazards regression was used to assess the association between treatment and risk of BCRL.**

Results: **Some 27·1 per cent of all patients (74 of 273) developed BCRL over the study period. Administration of taxanes showed a strong association with the development of BCRL, as 52 (33·5 per cent) of 155 patients who received taxanes developed BCRL. Multivariable Cox regression analysis demonstrated that patients who received taxanes were nearly three times more likely to develop BCRL than patients who had no chemotherapy (hazard ratio 2·82, 95 per cent c.i. 1·31 to 6·06). No such increase was observed when taxanes were administered in the neoadjuvant setting.**

Conclusion: **The present findings suggest that adjuvant taxanes play a key role in the development of BCRL after surgery. This may support the use of taxanes in a neoadjuvant rather than adjuvant setting.**

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Introduction

Lymphoedema is defined as the progressive accumulation of protein-rich fluid in interstitial spaces[1]. Breast cancer-related lymphoedema (BCRL) is a common complication of breast cancer treatment and is characterized by swelling in one or both arms, breast or trunk[2].

As surgical intervention has become more conservative, rates of BCRL have been decreasing. Patients undergoing sentinel lymph node biopsy (SLNB) have significantly lower rates of BCRL than those undergoing axillary lymph node dissection (ALND). The rate of BCRL in patients undergoing SLNB has been quoted as being as low as 4–6 per cent[3–5]. However, ALND is the surgical procedure of choice for patients with metastasis to axillary lymph nodes. In this group, the incidence of BCRL remains exceedingly high. Over a median follow-up of 9·5 years, Mortimer and colleagues[6] showed that 28 per cent of patients who had undergone ALND developed BCRL. A similar proportion (24 per cent) was reported by Schünemann and Willich[7], who followed 5657 patients over a median of 11 years. A meta-analysis[8] of 72 studies including 29 612 women estimated that 19·9 (range 8·4–21·4) per cent of patients undergoing ALND develop BCRL. Furthermore, it has been suggested that 75 per cent of BCRL cases occur within the first year after surgery, and 90 per cent within 3 years[9].

The great variability in rates of BCRL is due to the lack of an agreed definition in the literature, and a standardized and reliable method of quantifying BCRL[8,10]. Among

the quantitative measurements of BCRL, the most widely used is assessment of size, based on either circumference or direct measurement of arm volume. Water displacement is one of the earliest recorded methods of volume measurement, and is sometimes thought of as the standard, with good reproducibility. However, this method is time-consuming and cumbersome, which limits its routine clinical use. It is also contraindicated in patients with open skin lesions, and does not provide data about localization of the oedema and shape of the extremity[11]. The Perometer® (Pero-System, Wuppertal, Germany) is a device that uses infrared light-emitting diodes to calculate the volume of the arm. The shape of the limb is also recorded and displayed graphically, and can be used to measure the volume of any part of the limb[12,13]. The Perometer® has been evaluated comprehensively and its use is increasingly becoming the new standard procedure[10,13,14]. However, the diagnosis of BCRL cannot be based solely on a comparison of limb volumes, and women reporting self-perceived arm lymphoedema, regardless of the presence of objectively measured lymphoedema, have decreased long-term health-related quality of life[15]. Hence, this study used both objective and subjective criteria for the diagnosis of BCRL.

BCRL following breast cancer surgery remains a poorly understood process[16]. The initial treatment to the axilla, through either surgery or radiotherapy, is generally believed to be the catalyst in the development of BCRL; however, the majority of patients do not develop lymphoedema. More extensive axillary surgery and higher body mass index have long been identified as major risk factors for the development of BCRL[8]. Nevertheless, the aetiology of the condition remains incompletely defined and factors other than the primary initiating events have yet to be identified[17]. Adjuvant radiotherapy and systemic therapy have also been reported to increase the risk of developing BCRL, and several studies[18–21] have described an association between BCRL and adjuvant chemotherapy. Understanding of breast cancer has changed considerably over the past 40 years, with a shift towards it being treated as a systemic disease rather than a purely local disease. This change has led to a shift towards more conservative surgical and radiotherapy approaches, and an increased emphasis on systemic therapy involving cytotoxic drugs, hormones and biological response modifiers. In light of this, understanding the role that systemic therapy plays in the pathophysiology of BCRL is of crucial importance.

The aim of this retrospective cohort study was to determine risk factors for BCRL in consecutive patients treated with ALND, with a specific focus on the potential impact of chemotherapy on risk of BCRL. The hypothesis was that systemic adjuvant treatment represents a risk factor for the development of BCRL, and that taxane-based chemotherapy in the adjuvant setting is associated with a higher incidence of BCRL.

Methods

All patients diagnosed with breast cancer who underwent ALND at Guy's Hospital (a major London teaching hospital and part of King's Health Partners Academic Health Science Centre) between 1 January 2010 and 31 December 2012 were included in this study. Prospectively collected data were retrieved from electronic patient records, including: demographics, type of surgery, tumour characteristics (size, type, grade, hormone receptor status and human epidermal growth factor receptor 2 status, presence or absence of lymphovascular invasion (LVI)), lymph node status, adjuvant radiotherapy (including radiotherapy to the supraclavicular fossa (SCF)), endocrine therapy, type and timing of chemotherapy (adjuvant *versus* neoadjuvant), and diagnosis of BCRL. Data on Ki-67 were not available as this proliferation marker is not measured routinely at the centre.

All patients were discussed at a multidisciplinary team meeting, and those deemed at high risk of systemic recurrence were reviewed by the oncology team for consideration of neoadjuvant or adjuvant systemic therapy as well as adjuvant radiotherapy.

Diagnosis of breast cancer-related lymphoedema

The diagnosis of BCRL was based on subjective and/or objective criteria and documented in the medical record. BCRL was diagnosed if patients showed any of the following in the arm or hand: reduced visibility of the subcutaneous veins compared with those in the contralateral upper limb; thicker skin and subcutis; loss of the normal contours in the medial elbow/distal upper arm region; and pitting oedema. Arm volumes were quantified using a Perometer® 350S. Volume was measured between the ulna styloid process and the anterior axillary fold of both arms. From the perometry measurements, BCRL was determined by the presence of an arm volume difference of 10 per cent or more between the arm measurements of the affected and contralateral side. However, it should be noted that BCRL does not always manifest as an increase in arm volume alone, and in cases of mild BCRL the arm volume increase may not appear significant. In addition, there is also a natural asymmetry in arm volume depending on dominance, with the dominant arm being 3–5 per cent bigger than the non-dominant arm[12,22].

Table 1 Patient characteristics by breast cancer-related lymphoedema status

	No BCRL ($n = 199$)	BCRL ($n = 74$)
Age (years)*	58·5(13·8)	56·7(12·8)
No. of lymph nodes removed*	14·2(5·8)	13·2(5·6)
No. of positive nodes*	3·4(4·2)	4·4(6·2)
Tumour size (mm)*	38·4(35·3)	39·2(30·4)
Duration of follow-up (years)*	2·67(0·83)	0·85(0·67)
Taxanes	103 (51·8)	52 (70)
Chemotherapy	126 (63·2)	60 (81)
Timing of chemotherapy		
None	73 (36·7)	14 (19)
Neoadjuvant	54 (27·1)	15 (20)
Adjuvant	70 (35·2)	45 (61)
Both	2 (1·0)	0 (0)
Surgery type		
Mastectomy	120 (60·3)	45 (61)
Wide local excision	79 (39·7)	29 (39)
Tumour grade		
1	14 (7·0)	3 (4)
2	108 (54·3)	38 (51)
3	73 (36·7)	33 (45)
Unknown	4 (2·0)	0 (0)
Histological tumour type		
NST	149 (74·9)	62 (84)
Lobular	15 (7·5)	4 (5)
Other	35 (17·6)	8 (11)
Lymphovascular invasion		
No	115 (57·8)	34 (46)
Yes	83 (41·7)	40 (54)
Unknown	1 (0·5)	0 (0)
Oestrogen receptor status		
Negative	22 (11·1)	9 (12)
Positive	158 (79·4)	62 (84)
Unknown	19 (9·5)	3 (4)
HER2 status		
Negative	163 (81·9)	60 (81)
Positive	35 (17·6)	14 (19)
Unknown	1 (0·5)	0 (0)
Hormone therapy		
None	45 (22·6)	14 (19)
Tamoxifen	63 (31·7)	26 (35)
Anastrazole	3 (1·5)	3 (4)
Letrozole	45 (22·6)	9 (12)
Aromatase inhibitor switch	41 (20·6)	21 (28)
Unknown	2 (1·0)	1 (1)
Herceptin		
No	161 (80·9)	60 (81)
Yes	32 (16·1)	14 (19)
Unknown	6 (3·0)	0 (0)
Radiotherapy		
No	28 (14·1)	10 (14)
Yes	164 (82·4)	61 (82)
Unknown	7 (3·5)	3 (4)
SCF radiotherapy		
No	112 (56·3)	36 (49)
Yes	79 (39·7)	34 (46)
Unknown	8 (4·0)	4 (5)
Axillary radiotherapy		
No	198 (99·5)	73 (99)
Yes	1 (0·5)	1 (1)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). BCRL, breast cancer-related lymphoedema; NST, invasive tumour of no special type; HER2, human epidermal growth factor receptor 2; SCF, supraclavicular fossa.

Statistical analysis

Multivariable Cox proportional hazards regression was used to assess the association between taxane-based chemotherapy and the risk of BCRL. To gain further insight into the possible role of timing of chemotherapy, a stratified analysis for women treated with adjuvant and neoadjuvant chemotherapy was conducted. All models were adjusted for age, number of positive lymph nodes resected, and SCF radiotherapy. All analyses were conducted with SAS® release 9.3 (SAS Institute, Cary, North Carolina, USA).

Results

Of the 273 patients included in this analysis, 74 (27·1 per cent) developed BCRL over a mean follow-up of 2·67 years (*Table 1*). In all, 108 patients (39·6 per cent) underwent breast conservation, whereas 165 (60·4 per cent) were treated by mastectomy. Twenty-nine patients (26·9 per cent) who underwent wide local excision developed lymphoedema, compared with 45 (27·3 per cent) of those who underwent mastectomy.

Breast cancer-related lymphodema and tumour characteristics

In analysis of tumour characteristics, only the presence of LVI showed a statistically significant association with the onset of BCRL. Some 40 (32·5 per cent) of 123 patients with LVI developed BCRL, compared with 34 (22·8 per cent) of 149 without LVI. The relative risk for BCRL in the presence of LVI was 2·96 (95 per cent c.i. 2·16 to 4·07). Interestingly, the number of involved lymph nodes did not increase the risk of developing BCRL; 53 (27·0 per cent) of 196 patients with between one and three involved nodes developed BCRL, compared with 21 (27 per cent) of 77 with four or more involved lymph nodes.

(Neo)adjuvant treatment and breast cancer-related lymphoedema

A total of 211 patients (77·3 per cent) received adjuvant endocrine treatment (either tamoxifen, aromatase inhibitor

Table 2 Patient characteristics by chemotherapy status

	No chemotherapy ($n = 87$)	Chemotherapy with taxanes ($n = 155$)	Chemotherapy without taxanes ($n = 31$)
Age (years)*	71·5(12·7)	50·2(10·1)	56·4(11·5)
No. of nodes removed*	14·2(5·9)	13·7(4·7)	14·2(7·2)
No. of positive nodes*	2·8(3·8)	4·0(4·7)	4·9(7·5)
Tumour size (mm)*	25·2(13·2)	43·6(28·2)	38·7(50·6)
Duration of follow-up (years)*	2·33(1·15)	2·04(1·09)	2·36(1·24)
BCRL	14 (16)	52 (33·5)	8 (26)
Timing of chemotherapy			
None	87 (100)	0 (0)	0 (0)
Neoadjuvant	0 (0)	64 (41·3)	5 (16)
Adjuvant	0 (0)	90 (58·1)	25 (81)
Both	0 (0)	1 (0·6)	1 (3)
Surgery type			
Mastectomy	48 (55)	102 (65·8)	15 (48)
Wide local excision	39 (45)	53 (34·2)	16 (52)
Tumour grade			
1	9 (10)	6 (3·9)	2 (6)
2	53 (61)	78 (50·3)	15 (48)
3	23 (26)	69 (44·5)	14 (45)
Unknown	2 (2)	2 (1·3)	0 (0)
Histological tumour type			
NST	61 (70)	123 (79·4)	27 (87)
Lobular	9 (10)	8 (5·2)	2 (6)
Other	17 (20)	24 (15·5)	2 (6)
Lymphovascular invasion			
No	60 (69)	78 (50·3)	11 (35)
Yes	27 (31)	76 (49·0)	20 (65)
Unknown	0 (0)	1 (0·6)	0 (0)
Oestrogen receptor status			
Negative	5 (6)	20 (12·9)	6 (19)
Positive	80 (92)	119 (76·8)	21 (68)
Unknown	2 (2)	16 (10·3)	4 (13)
HER2 status			
Negative	82 (94)	113 (72·9)	28 (90)
Positive	4 (5)	42 (27·1)	3 (10)
Unknown	1 (1)	0 (0)	0 (0)
Hormone therapy			
None	11 (13)	38 (24·5)	10 (32)
Tamoxifen	12 (14)	71 (45·8)	6 (19)
Anastrazole	3 (3)	2 (1·3)	1 (3)
Letrozole	30 (34)	19 (12·3)	5 (16)
Aromatase inhibitor switch	29 (33)	25 (16·1)	8 (26)
Unknown	2 (2)	0 (0)	1 (3)
Herceptin			
No	85 (98)	108 (69·7)	28 (90)
Yes	0 (0)	44 (28·4)	2 (6)
Unknown	2 (2)	3 (1·9)	1 (3)
Radiotherapy			
No	23 (26)	11 (7·1)	4 (13)
Yes	58 (67)	141 (91·0)	26 (84)
Unknown	6 (7)	3 (1·9)	1 (3)
SCF radiotherapy			
No	65 (75)	63 (40·6)	20 (65)
Yes	17 (20)	86 (55·5)	10 (32)
Unknown	5 (6)	6 (3·9)	1 (3)
Axillary radiotherapy			
No	87 (100)	154 (99·4)	30 (97)
Yes	0 (0)	1 (0·6)	1 (3)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). BCRL, breast cancer-related lymphoedema; NST, invasive tumour of no special type; HER2, human epidermal growth factor receptor 2; SCF, supraclavicular fossa.

Table 3 Multivariable Cox proportional hazards age-adjusted analysis of risk of breast cancer-related lymphoedema by chemotherapy status among women who underwent axillary lymph node dissection

	Hazard ratio		
	Model 1	Model 2	Model 3
Chemotherapy			
No	1·00 (reference)	1·00 (reference)	1·00 (reference)
Yes, with taxanes	2·90 (1·35, 6·22)	2·82 (1·31, 6·06)	2·89 (1·32, 6·33)
Yes, without taxanes	1·93 (0·77, 4·89)	1·64 (0·62, 4·32)	1·67 (0·63, 4·40)
No. of positive lymph nodes		1·03 (0·99, 1·08)	1·04 (0·99, 1·09)
SCF radiotherapy			
No			1·00 (reference)
Yes			0·92 (0·55, 1·57)
Unknown			1·49 (0·53, 4·21)

Values in parentheses are 95 per cent c.i. Model 1, chemotherapy alone; model 2, chemotherapy plus number of involved lymph nodes; model 3, chemotherapy status plus number of involved nodes and supraclavicular fossa (SCF) radiotherapy status.

(AI) or AI switch). Of these, 59 (28·0 per cent) developed BCRL. Of the 59 patients who did not receive adjuvant endocrine treatment, 14 (24 per cent) developed BCRL (*Table 1*).

In all, 113 patients (41·4 per cent) received radiotherapy to the SCF. Of these, 34 (30·1 per cent) developed BCRL, compared with 36 (24·3 per cent) of those who did not receive SCF treatment (*Table 1*). SCF radiotherapy had a relative risk of BCRL of 1·23 (95 per cent c.i. 0·81 to 1·89) compared with no SCF irradiation, but this was not significant.

A total of 186 patients (68·1 per cent) were treated with chemotherapy in either the neoadjuvant (69, 37·1 per cent) or adjuvant (115, 61·8 per cent) setting; two patients had chemotherapy in both settings (*Table 2*). In all, 14 (16 per cent) of those who did not receive chemotherapy developed BCRL, compared with 60 (32·3 per cent) of the patients who received chemotherapy. A more detailed breakdown of this group shed further light on the effect of chemotherapy. Of the 60 patients who developed BCRL following chemotherapy, 52 received taxanes and eight did not. Fifty-two (33·5 per cent) of 155 patients who received taxanes developed BCRL, compared with eight (26 per cent) of 31 patients who received a regimen that did not include taxanes (*Table 2*).

Further analysis of the taxane group showed that 64 women were treated in the neoadjuvant setting, whereas 90 received adjuvant taxanes. One patient underwent both neoadjuvant and adjuvant taxane chemotherapy. In all, 13 (20 per cent) of 64 patients who received neoadjuvant taxanes went on to develop BCRL, compared with 39 (43 per cent) of 90 treated in the adjuvant setting.

Table 4 Multivariable Cox proportional hazards age-adjusted analysis of risk of breast cancer-related lymphoedema by chemotherapy status and by timing of chemotherapy among women who underwent axillary lymph node dissection

	Hazard ratio		
	Model 1	Model 2	Model 3
Neoadjuvant chemotherapy			
Taxanes			
No	1·00 (reference)	1·00 (reference)	1·00 (reference)
Yes	1·18 (0·15, 8·95)	0·85 (0·11, 6·70)	0·81 (0·09, 7·34)
No. of positive lymph nodes		0·91 (0·80, 1·05)	0·91 (0·80, 1·05)
SCF radiotherapy			
No			1·00 (reference)
Yes			1·12 (0·33, 3·83)
Adjuvant chemotherapy			
Taxanes			
No	1·00 (reference)	1·00 (reference)	1·00 (reference)
Yes	1·90 (0·81, 4·48)	1·94 (0·77, 4·88)	1·90 (0·76, 4·78)
No. of positive lymph nodes		1·10 (1·04, 1·16)	1·13 (1·06, 1·20)
SCF radiotherapy			
No			1·00 (reference)
Yes			0·63 (0·29, 1·35)
Unknown			0·79 (0·19, 3·37)

Values in parentheses are 95 per cent c.i. Model 1, chemotherapy alone; model 2, chemotherapy plus number of involved lymph nodes; model 3, chemotherapy status plus number of involved nodes and supraclavicular fossa (SCF) radiotherapy status.

Analysis of the risk of BCRL by chemotherapy status showed that women receiving taxanes were nearly three times more likely to develop BCRL than those who had no chemotherapy (hazard ratio (HR) 2·82, 95 per cent c.i. 1·31 to 6·06) (*Table 3*). No such increase was observed for taxanes given in the neoadjuvant setting; a comparison of neoadjuvant taxanes *versus* no chemotherapy did not show a significantly increased risk for BCRL (HR 1·26, 0·59 to 2·67). On stratification by timing of chemotherapy (adjuvant *versus* neoadjuvant), women receiving taxanes in the adjuvant setting were nearly twice as likely to develop BCRL than patients receiving non-taxane-based adjuvant chemotherapy (HR 1·94, 0·77 to 4·88), although this did not reach statistical significance (*Table 4*).

Discussion

ALND has been identified as the most significant risk factor for developing BCRL, with an incidence greater than 20 per cent, compared with less than 10 per cent in patients undergoing SLNB[8,23–27]. Adjuvant radiotherapy and systemic therapy have also shown a correlation with the development of BCRL. A few studies[13–16,28] have reported an association between BCRL and adjuvant chemotherapy.

In this retrospective series of 273 consecutive patients who received ALND as part of breast cancer treatment, the cumulative incidence of BCRL was 27·1 per cent. Administration of taxanes as part of the chemotherapy regimen showed a strong association with the development of subsequent BCRL, as 33·5 per cent of patients who received taxane-based chemotherapy developed BCRL. More specifically, taxanes administered in the adjuvant setting proved to be the strongest risk factor for BCRL, with 43 per cent of these patients developing BCRL. Multivariable Cox regression analysis confirmed that patients who received taxanes after ALND were nearly three times more likely to develop BCRL than those who did not receive chemotherapy.

In a study of 631 patients, Norman and colleagues[29] also found that patients receiving anthracycline-based chemotherapy were more likely to develop BCRL than those who did not have chemotherapy (HR 1·46, 95 per cent c.i. 1·04 to 2·04). In multivariable analysis, the combination of ALND and chemotherapy increased the hazards ratio 4–5-fold for BCRL. The present data did not show a statistically significant increase in risk of BCRL among patients receiving non-taxane-based chemotherapy regimens, although this could be related to the small number of patients who received such treatment in the present cohort.

Taxanes have emerged as important chemotherapeutic drugs in the treatment of patients with breast cancer. Paclitaxel (Taxol®; Bristol-Myers Squibb, New York, USA) is isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) and docetaxel (Taxotere®; Sanofi Aventis, Paris, France) is synthesized from the needles of the European yew tree (*T. baccata*). They both have similar chemical structures, which bind to tubulin, stabilize microtubules and cause inhibition of cell division. They are used in adjuvant, neoadjuvant and metastatic settings[30,31]. Taxane-based chemotherapy has been shown to improve disease-free and overall survival in early operable breast cancer[31–33].

The association of taxanes with the development of peripheral oedema has been reported previously. Early clinical trials involving docetaxel observed progressive development of peripheral oedema and non-malignant effusions, which could be severe enough to warrant discontinuation of therapy[34,35]. The peripheral oedema was typically localized to the upper and lower limbs, but could also spread to the trunk. It appeared to be related to the cumulative dose of docetaxel, and concurrent prophylactic corticosteroids were recommended during treatment to decrease symptoms. A suggested mechanism of action was that repeated docetaxel exposure induced endothelial inflammation leading to abnormal capillary permeability[36,37]. An investigation[37] into the mechanism of the development of oedema in patients receiving taxanes, conducted with capillaroscopy and capillary filtration tests using ^{99m}Tc-labelled albumin, concluded that there was an abnormality in capillary permeability and also progressive accumulation of proteins in the interstitial space. A study[36] using the wick and wick-in-needle method to assess transcapillary forces also confirmed treatment-induced capillary protein leakage. Lee and colleagues[38] recently published a small prospective cohort study involving 63 women recruited after axillary lymph node surgery. Some 53 of these patients received taxanes in the postoperative setting. They observed an increase in the extracellular fluid volume in both upper and lower limbs, which was not observed after anthracycline-based chemotherapy. The arm on the ipsilateral side of surgery was affected preferentially, indicated by increased extracellular fluid ratios at 3 weeks and 6 months after completion of taxane-based chemotherapy. Oedema resolved by 6 months following completion of chemotherapy except in the arm on the side of surgery[38]. This observation is in line with the data reported here and supports a key role of taxanes in the pathogenesis of BCRL. Taxanes may cause systemic disruption, which could have a longer-term effect on lymphatic function[28].

Some experimental models have shown evidence of neolymphangiogenesis following disruption of lymphatic drainage in limbs[39,40]. Recent studies suggest that lymphangiogenesis can be stimulated by various cytokines. For example, vascular endothelial growth factor (VEGF) C and VEFG-D promote lymphangiogenesis by activating VEGF receptor 3, which is expressed on lymphatic endothelial cells[41]. VEGF-C-deficient mice fail to develop a functional lymphatic system[42], and gene transfer of VEGF-C reduced lymphoedema effectively in an animal model[43]. Of note, taxanes have been shown in several experimental models to inhibit neolymphangiogenesis by suppressing the VEGF molecule family members, especially VEGF-A, -C and -D[44,45].

Chronic oedema is the result of a balance between microvascular filtration and lymph drainage. Increased vascular permeability will result in increased microvascular filtration and therefore increased lymph flow. If lymph flow cannot increase, a decompensated state will arise causing oedema. Taxanes have been shown to increase vascular permeability, which in the adjuvant setting overwhelms compromised lymph drainage routes. Therefore, it can be hypothesized that taxanes may also induce a failure in neolymphangiogenesis, which would otherwise have been expected to take place following disruption to lymphatics caused by surgery.

In the present cohort, adjuvant taxane-based chemotherapy following ALND was a strong independent risk factor for the development of BCRL. The administration of taxanes conveyed a nearly threefold increase in the risk of developing BCRL, predominantly in the adjuvant setting. In view of the experimental evidence detailed above, this observation could be explained by the hypothesis that adjuvant taxanes exert an antilymphangiogenic effect, thereby inhibiting a process of lymphatic regeneration that might otherwise limit or prevent the development of BCRL.

The results of this hypothesis-generating study also support the observation that adjuvant taxane-based chemotherapy is more deleterious than neoadjuvant taxane-based chemotherapy. Neoadjuvant administration of taxanes could potentially reduce the incidence of BCRL, which should be verified in a randomized clinical trial.

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