Regional and seasonal influence in patient's toxicity to adjuvant chemotherapy for early breast cancer

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Abstract:

Introduction: Results from multinational clinical trials are globally adopted into the routine clinical practice in most countries. Changes in the natural history and incidence of certain diseases as well as in drugs toxicities related to yearly seasons have been reported, however, variations related to climate have never been described. In our study, we assessed whether yearly seasons and climate could influence the chemotherapy toxicity profile.

Methods: We analyzed the toxicities recorded in the phase III GEICAM 9906 study which was run in different geographically and climatically/seasonally regions in Spain. In this trial 1246 patients were randomized and eligible to receive FEC90 x6 cycles or FEC90 x4 cycles followed by 8 doses of weekly paclitaxel (T).

Results: The results showed differences in hematological and non-hematological toxicities in relation to the season of the year and the climate of the area in which the treatment was administered. We found a higher hematological toxicity in warm seasons (spring and summer) and in Oceanic climate regions (Neutropenia G4: 7.8 vs 1.0 vs 1.0%, $p<0.0001$). Asthenia was greater frequency in the summer period (FEC90: 21.1%, T: 15.3%) as well as in the Mediterranean areas (FEC: 28% T: 27.2%). Also we observed, liver transaminase elevations were more frequent in the summer and in the Oceanic areas. Myalgias and secondary sensory neuropathy to paclitaxel were recorded more frequently during autumn.

Conclusion: Climate should be considered a significant variable in toxicity to chemotherapy.

[Abstract word count = 236]

Introduction

Chemotherapy is an integral part in the therapeutic management of the majority of tumour types. Efficacy and safety are assessed in clinical trials which are often conducted in several countries. The communication and diffusion of the results are globalized, as are the therapeutic attitudes and treatment regimens. However, there are variables in different countries and geographical areas which can have an influence on trial outcomes and, as such, need to be taken into account in the data analyses. One of these variables is climate.

Variations in the incidence of diseases related to the yearly seasonal stages have been published [1]. These include the incidence of cardiovascular [2] and cerebrovascular disease with a peak incidence during the winter [3, 4] and infectious disease [5]. In oncology, there have been reports of seasonal differences in lymphoma [6] breast cancer [7, 8] and other tumour types [9].

Relationships between the season of the year and the natural history of the disease have been also published. A Norwegian prostate cancer study showed better prognosis in patients who were diagnosed during the summer and the autumn [10]. Also in Norwegian patients, there were differences in lung cancer incidence; the authors postulated that the underlying cause of this prognostic variation was the physiological modifications produced as a result of the differences in the levels of exposure to vitamin D [11, 12].

Similarly, there have been descriptions of seasonal changes in the activity of some enzymatic systems responsible for the metabolism of substances and toxins, which can result in toxicity variations to specific drugs. As an example, the hepatic toxicity induced by tetracyclines in an animal model was greater in winter and autumn due to a decrease in the levels of toxin conjugation and excretion by the liver [13]. Also described in another murine model was the circadian and seasonal variation in the nephrotoxicity induced by amikacin and gentamicin, and the haematological toxicity induced by adriamycin and epirubicin [14-17].

Experimental carcinogenesis studies performed in animals showed that the success in the tumours induction varied as a function of the season of the year. For example, 56 and 61% of Sprague-Dawley rats developed breast cancer when exposed to DMBA in the spring and summer, while only 24% develop the tumors if induced in the autumn [18].

Cytostatic drugs used in the treatment of cancer are characterized by narrow therapeutic margins. Slight modifications can have an impact on the toxicity profile and, as such, could affect the conditions of the drugs' employment. To-date, there have not been any publications addressing the influence of climate on chemotherapy toxicity.

Patients and Methods

We analyzed the toxicities recorded in the GEICAM 9906 study (19). This trial included 1246 patients recruited in 65 Spanish hospitals. Patients were randomized to receive FEC90 (5-fluorouracil 600mg/m2, epirubicin 90 mg/m2, cyclophosphamide 600 mg/m2) for 6 cycles every 21 days; or sequential FEC90 for 4 cycles every 21 days followed by weekly paclitaxel (100 mg/m2) for 8 weeks. 10.780 cycles were administered, 6.191 of FEC90 and 4,589 of paclitaxel.

The hematological and non-hematological toxicities were assessed in relation to climate (seasonal) and geographical areas. The seasons were defined as: spring (from 21st March to 21st June), summer (from 22nd June to 23rd September), autumn (from 24th September to 21st December) and winter (from 22nd December to 20th March). The geography-affected climate areas were defined according to the information provided in the Spanish Education Ministry web page [20]. They were classified as: Oceanic (characterized by mild temperatures throughout the year [10-20ºC] and corresponding to the Regions of Galicia, Cantabria and Basque Country); Mediterranean (characterized as high temperatures in summer and mild in winter and corresponding to the Regions of Catalunya, Balearic Islands, Valencia, Murcia, Andalucia including Almeria, Malaga, Sevilla, Huelva and Cadiz); Continental (characterized by extremes temperatures, and corresponding to the Regions of Castilla la Mancha, Aragon, Navarra, Extremadura, Castilla-Leon and Andalucia including Granada, Cordoba and Jaen) and Sub-tropical (characterized by temperatures between 18-25ºC throughout the year, and

corresponding to the Canary Islands). This last geographic area was excluded from the current analyses because the original study had very few patients recruited from there.

Recorded toxicities were segregated according to the different seasons and Geographic-climatic areas. Contingency tables were used to compare the toxicity vs the season as well as the toxicity vs the climate area in a separate analysis. The $\chi 2$ test was used to check the hypothesis that the two variables were independent in each analysis separatelly. Statistical significance was set at $p<0.05$.

Results

We analyzed all toxicities by grade for both treatment arms and distributed them by the seasons of the year (Table 1) and by Geographic-climate areas (Table 2). Toxicity items and grades were different between the regimens and the tables because only the statistically significant differences in toxicities were included.

In general, the statistically significant differences observed were only in low grade toxicities (except for neutropenia and vomiting).

The results showed statistically significant differences for some of the toxicities related to the season of the year and the Geographic-climate area where the patients were treated. We observed a higher hematological toxicity with both FEC90 and paclitaxel in warm seasons (spring and summer) and in Oceanic climate regions. Asthenia was a symptom that occurred with greater frequency in the summer period, as well as in the Mediterranean areas. Liver transaminase elevations were more frequent in the summer and in the Oceanic areas. Myalgias and secondary sensory neuropathy to paclitaxel were recorded more frequently during autumn.

Commentary:

Internationalization of clinical research has resulted in globalization of therapeutic approaches and regimens. Changes in the incidence and intensity of toxicities to several drugs in relation with the yearly seasons have been reported in animal models. However, seasonal and climate differences in chemotherapy toxicity in patients have not been described yet.

We have seen that the tolerability of a specific drug or treatment regimen could be affected by the yearly seasons and the climate conditions in which the treatment is administered. Differences in toxicity can lead to differences in dose reductions. Bonadonna et al showed a dose-response effect to chemotherapy when administered in the adjuvant setting to patients with breast cancer [21]. When CMF was administered at full or almost full doses (greater than or equal to 85%) patients had a five-year disease free survival of 77%, in contrast, only 67% of patients were disease free at five year when only 65% of the planned doses were administered. Based on the results observed in the current work, and knowing the slim therapeutic margin of chemotherapy, drug efficacy could potentially be affected by climatic conditions. Due to that, the toxicity analysis as a function of climate variables should be taken into account when data from clinical trials are reviewed.

[Text word count = 1125 words, without tables]

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Table 1. Patient's toxicities related to the season of the year*

		Spring	Summer	Autumn	Winter	p
Toxicity	Grade	N(%)	N(%)	N(%)	N(%)	
FEC90 every 21 days (5FU: 600mg/m^2+4EPI 90mg/m^2+cyclophosphamide 600mg/m^2) N= 6191 cycles						
		N=1864	N=1583	N=1211	N=1533	
Hemoglobin	G1	769(41.3)	675(42.6)	465(38.4)	587(38.3)	0.034
Leukocytes	G1	322(17.3)	312(19.7)	202(16.7)	319(20.8)	0.0102
Neutrophils	G4	24(1.3)	48(3.0)	39(3.2)	42(2.7)	0.001
Asthenia	G1	283(15.2)	267(16.9)	156(12.9)	228(14.9)	0.0354
Diarrhea	G1	48(2.6)	46(2.9)	28(2.3)	20(1.3)	0.0186
	G2	19(1)	20(1.3)	15(1.2)	4(0.3)	0.0135
Stomatitis	G2	158(8.5)	131(8.3)	96(7.9)	91(5.9)	0.0276
Vomiting	G3	36(1.9)	49(3.1)	32(2.6)	22(1.4)	0.0093
Alkaline phosphatase	G1	54(2.9)	40(2.5)	54(4.5)	46(3.0)	0.0248
SGOT/AST	G2	18(1.0)	8(0.5)	22(1.8)	18(1.2)	0.0092
SGPT/ALT	G1	362(19.4)	293(18.5)	268(22.1)	263 (17.2)	0.0098
Infection without neutropenia	G1	30(1.6)	31(2)	36(3.0)	57(3.7)	0.0003
Hypercholesterolemia	G1	15(0.8)	2(0.1)	3(0.2)	7(0.5)	0.0159
Insomnia	G1	4(0.2)	9(0.6)	9(0.7)	15(1.0)	0.0321
Mood alteration-anxiety	G1	9(0.5)	22(1.4)	8(0.7)	8(0.5)	0.0091
Paclitaxel 100 mg/m2 weekly; N=4589 cycles						
		N=1206	N=1375	N=1126	N=882	p
Allergic reaction/hypersensitivity	G1	9(0.7)	7(0.5)	5(0.4)	17(1.9)	0.0008
Hemoglobin	G1	778(64.5)	853(62)	682(60.6)	495(56.1)	0.0013
	G2	85(7.0)	167(12.1)	87(7.7)	63(7.1)	<0.0001
Leukocytes	G1	271(22.5)	358(26.0)	294(26.1)	252(28.6)	0.0142
	G2	19(1.6)	18(1.3)	5(0.4)	17(1.9)	0.019
Neutrophils	G3	24(2.0)	12(0.9)	7(0.6)	6(0.7)	0.0035
Asthenia	G1	178(14.8)	210(15.3)	165(14.7)	97(11)	0.0263
Injection site reaction	G1	24(2.0)	14(1.0)	16(1.4)	24(2.7)	0.015
Nail changes	G1	74(6.1)	53(3.9)	65(5.8)	46(5.2)	0.0468
Pruritos	G1	15(1.2)	16(1.2)	25(2.2)	27(3.1)	0.0026
Rash/desquamation	G1	73(6.1)	39(2.8)	70(6.2)	55(6.2)	<0.0001
Nauseas	G1	50(4.1)	42(3.1)	25(2.2)	18(2.0)	0.0132
Epistaxis	G1	17(1.4)	5(0.4)	18(1.6)	27(3.1)	<0.0001
Alkaline phosphatase	G1	19(1.6)	35 (2.5)	45(4.0)	11(1.2)	0.0001

GGT	G1	12(1)	49(3.6)	18(1.6)	9(1)	<0.0001
SGOT/AST	G1	107(8.9)	176(12.8)	146(13)	107(12.1)	0.0049
SGPT/ALT	G1	266(22.1)	369(26.8)	215(19.1)	232(26.3)	<0.0001
Hyperuricemia	G1	1(0.1)	11(0.8)	10(0.9)	9(1.0)	0.0299
Depressed level of Consciousness	G1	8(0.7)	9(0.7)	2(0.2)	15(1.7)	0.0011
Mood alteration- anxiety	G1	6(0.5)	2(0.1)	15(1.3)	7(0.8)	0.0027
Sensory neuropathy	G1	241(20)	279(20.3)	280(24.9)	170(19.3)	0.0051
	G2	47(3.9)	70(5.1)	86(7.6)	33(3.7)	<0.0001
Motor neuropathy	G2	2(0.2)	9(0.7)	6(0.5)	10(1.1)	0.0397
Myalgias	G1	112(9.3)	128(9.3)	148(13.1)	95(10.8)	0.0062

*Only statistically significant differences in toxicities are included

Table 2. Patient's toxicities related to Geographic-climate area*.

		Oceanic	Mediterranean	Continental	P
Toxicity	Grade	N(%)	N(%)	N(%)	
FEC90 every 21 days (5FU: 600mg/m^2+4EPI 90mg/m^2+cyclophosphamide 600mg/m^2) N= 6033 cycles					
		N=1294	N=2858	N=1881	
Hemoglobin	G1	614(47.4)	1155(40.4)	681(36.2)	<0.0001
	G2	63(4.9)	128(4.5)	57(3.0)	0.0147
Leukocytes	G1	281(21.7)	506(17.7)	349(18.6)	0.0086
	G2	140(10.8)	194(6.8)	77(4.1)	<0.0001
	G3	106(8.2)	60(2.1)	18(1.0)	<0.0001
Neutrophils	G1	175(13.5)	298(10.4)	234(12.4)	0.0081
	G2	130(10.0)	221(7.7)	117(6.2)	0.0004
	G3	130(10.0)	148(5.2)	74(3.9)	<0.0001
	G4	101(7.8)	30(1.0)	19(1.0)	<0.0001
Platelets	G1	22(1.7)	27(0.9)	36(1.9)	0.0131
Phlebitis	G2	16(1.2)	88(3.1)	34(1.8)	0.0003
Asthenia	G1	170(13.1)	549(19.2)	206(11.0)	<0.0001
	G2	113(8.7)	231(8.1)	112(6.0)	0.0050
	G3	2(0.2)	21(0.7)	8(0.4)	0.0432
Fever	G1	25(1.9)	87(3.0)	40(2.1)	0.045
Rash/desquamation	G1	24(1.9)	96(3.4)	30(1.6)	0.0002
Hot flashes/flushes	G1	15(1.2)	31(1.1)	7(0.4)	0.0174
Constipation	G1	50(3.9)	169(5.9)	55(2.9)	<0.0001
	G2	10(0.8)	54(1.9)	12(0.6)	0.0002
Dyspepsia/Heartburn	G1	48(3.7)	80(2.8)	41(2.2)	0.0371
	G2	1(0.1)	10(0.3)	15(0.8)	0.0064
Nauseas	G1	307(23.7)	869(30.4)	452(24.0)	<0.0001
	G2	160(12.4)	394(13.8)	294(15.6)	0.0288
	G3	6(0.5)	57(2.0)	25(1.3)	0.0006
Taste disturbance (dysgeusia)	G1	13(1.0)	98(3.4)	20(1.1)	<0.0001
Vomiting	G1	166(12.8)	458(16.0)	230(12.2)	0.0003
	G2	224(17.3)	309(10.8)	263(14.0)	<0.0001
SGOT/AST	G2	6(0.5)	39(1.4)	16(0.9)	0.0190
SGPT/ALT	G1	297(23.0)	495(17.3)	365(19.4)	0.0001
Paclitaxel 100 mg/m2 weekly; N=4461 cycles					
		N=1010	N=2082	N=1369	P
Allergic reaction/hypersensitivity	G1	4(0.4)	12(0.6)	22(1.6)	0.0011
Hemoglobin	G2	67(6.6)	237(11.4)	94(6.9)	<0.0001
Leukocytes	G2	150(14.9)	213(10.2)	109(8.0)	<0.0001
Neutrophils	G1	156(15.4)	247 (11.9)	181(13.2)	0.0213
	G2	107(10.6)	130(6.2)	67(4.9)	<0.0001
	G3	19(1.9)	19(0.9)	11(0.8)	0.0241
Edema	G1	31(3.1)	37(1.8)	9(0.7)	<0.0001
Asthenia	G1	109(10.8)	410(19.7)	128(9.3)	<0.0001
	G2	44(4.4)	135(6.5)	74(5.4)	0.0494
Injection site reaction	G1	9(0.9)	48(2.3)	21(1.5)	0.0146
Nail changes	G1	69(6.8)	115(5.5)	48(3.5)	0.001
Rash/desquamation	G1	70(6.9)	127(6.1)	39(2.8)	<0.0001
Constipation	G1	14(1.4)	64(3.1)	22(1.6)	0.0020
Diarrhea	G1	8(0.8)	51(2.4)	24(1.8)	0.0056

Nauseas	G1	22(2.2)	88(4.2)	24(1.8)	<0.0001
Stomatitis/pharyngitis	G2	5(0.5)	23(1.1)	32(2.3)	0.0003
Taste disturbance	G1	9(0.9)	55(2.6)	15(1.1)	0.00019
Epistaxis	G1	41(4.1)	10(0.5)	14(1.0)	<0.0001
Alkaline phosphatase	G1	54(5.3)	29(1.4)	26(1.9)	<0.0001
Bilirubin	G1	3(0.3)	41(2.0)	18(1.3)	0.0009
GGT	G1	37(3.7)	39(1.9)	12(0.9)	<0.0001
SGOT/AST	G1	123(12.2)	288(13.8)	117(8.5)	<0.0001
SGPT/ALT	G1	283(28.0)	474(22.8)	304(22.2)	0.0015
Hypercholesterolemia	G1	0(0.0)	11(0.5)	14(1.0)	0.0041
Hypertriglyceridemia	G1	0(0.0)	21(1.0)	6(0.4)	0.0020
Hyperuricemia	G1	0(0.0)	22(1.1)	9(0.7)	0.0040
Metabolic/Laboratory-Other(Specify, LDH)	G1	16(1.6)	3(0.1)	11(0.8)	0.00002
Depressed level of Consciousness	G1	17(1.7)	13(0.6)	4(0.3)	0.0004
Mood alteration- anxiety Agitation	G1	5(0.5)	21(1.0)	4(0.3)	0.0308
Motor neuropathy	G2	6(0.6)	6(0.3)	15(1.1)	0.0114
Conjunctivitis	G1	6(0.6)	46(2.2)	11(0.8)	0.0001
Arthralgias	G1	53(5.2)	198(9.5)	110(8.0)	0.0002
Myalgias	G1	104(10.3)	261(12.5)	116(8.5)	0.0007
Creatinine	G1	6(0.6)	31(1.5)	6(0.4)	0.0033

*Only statistically significant differences in toxicities are included