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Composition and production rate of cytostatic pharmaceutical waste from a Greek Cancer Treatment Hospital

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Abstract

The objective of this work was to determine the composition and production rate of cytostatic pharmaceutical waste produced by Theagenion Cancer Treatment Hospital (TCTH) in Thessaloniki, Greece. This information is necessary for the design and costing of management systems for cytostatic pharmaceutical waste, for assessing their environmental impact and for health and safety considerations. A total of 826 kg cytostatic pharmaceutical waste was collected, manually separated and weighed over a period of ten working weeks. Total cytostatic pharmaceutical waste was classified in three categories, vial waste comprising 38.3%, syringe waste with 4.5% and intravenous therapy (IV) waste with 57.2% of the total. Vial waste only was classified according to the active ingredients in alkylating agents, antimetabolites, cytotoxic antibiotics, Vinca alkaloids and "other" antineoplastic drugs. The overall cytostatic waste production by the hospital was 22900(6955) g/d, with numbers in parenthesis representing standard deviations. The average unit production rates of total cytostatic pharmaceutical waste were 140(64) g/patient/d and 201(61) g/bed/d. The respective unit production rates were: (1) for vial waste 41(11) g/patient/d and 77(46) g/bed/d, (2) for syringe waste 5(1.5) g/patient/d and 9(5) g/bed/d and (3) for IV waste 94(63) g/patient/d and 115(43) g/bed/d.

Keywords: Antineoplastic waste, vial waste, syringe waste, IV waste, unit production rate.

1. Introduction

The cytostatic drugs (also called antineoplastic drugs) are used for treatment of cancer. They influence the metabolism of cancer cells, thus, hindering their division and reproduction through different modes of action. There are more than 100 such drugs currently being used, which are administered to patients under controlled conditions at hospitals and consumed by out-patients at home (Eitel *et al.,* 1999; Johnson *et al.,* 2008; Zhang *et al.,* 2013; Franquet-Griell *et al.,* 2017). These compounds are consumed at quantities of tons per year. For example, the total consumption of antineoplastic pharmaceuticals in Spanish pharmacies in 2015 was 23.4 tons, with mycophenolic acid and hydroxycarbamide being the most prescribed (Franquet-Griell *et al.,* 2017).

Some undesired effects of cytostatic drugs include hair loss, nausea and immune system depression, for both treated cancer-patients and drug-handling personnel. Occupational exposure to some kinds of cytostatic pharmaceuticals may result in health problems, such as infertility, birth defects, miscarriage, skin rashes and possibly cancer (Department of Health and Human Services, 2004). In fact, some cytostatic drugs can potentially act as carcinogens, teratogens and/or mutagens (Allwood *et al.,* 2002; Zhang *et al.,* 2013).

Important sources of cytostatic drugs to the environment are the municipal and hospital wastewaters, which contain drugs and their metabolites in urine and feces from treated patients. There is limited information regarding the presence and fate of cytostatic drugs in the aquatic environment and even less in soil. For example, concentrations for specific cytostatic pharmaceuticals up to 100 ng/L were determined in hospital wastewater (al-Ahmad *et al.,* 1997; Steger-Hartmann *et al.,* 1996). Concentrations up to 17 ng/L in river water in South East England, for the cytostatic drug "Bleomycin" were reported by Aherne *et al.* (1990). Buerge *et al.* (2006) reported concentration of cyclophosphamide in wastewater treatment plant effluents in Switzerland ranging from 0.15 to 0.17 ng/L. Besse *et al.* (2012) presented data for anticancer drugs in surface waters in France. Kosjek and Heath (2011) discussed analytical methods for determination of cytostatic pharmaceuticals in the environment. Zhang *et al.* (2013) reviewed state-of-the-art technologies (including source separation) for effective treatment of wastewater containing cytostatic drugs. Environmental risk assessment is available for only a few cytostatic drugs, but not for their metabolites and transformation products, which are of major concern (Negreira *et al.,* 2014). There are even fewer studies addressing their genotoxicity risk assessment (Toolaram *et al.,* 2014).

The presence of pharmaceuticals in municipal solid waste (MSW) was reported by Musson and Townsend (2009). They estimated the concentration of active pharmaceutical ingredients in Florida MSW in the range 7.4 – 45 mg/kg MSW, but with no reference to cytostatics. Very likely, some of these materials will end up in landfill leachates and perhaps to surface and groundwaters (Kümmerer, 2009).

In general, the sources of pharmaceuticals in MSW could be illegal dumping of medical waste from healthcare facilities and discarding of unused or expired medicine to household waste. These are potentially significant but unknown sources. For example, approximately one third of pharmaceuticals sold in Germany and 25% of that sold in Austria is disposed of with household waste or down the drain (Kümmerer, 2009). The importance of these routes was also shown by a survey conducted in the UK (Bound and Voulvoulis, 2005). There are no data for cytostatic waste, in MSW.

In the European Union, cytostatic waste is classified in chapters 18 ("wastes from human or animal health care and/or related research") and 20 ["municipal wastes (household waste and similar commercial, industrial and institutional wastes) including separately collected fractions"] of the European Waste Catalogue (European Waste Catalogue, 2002). Specifically, cytotoxic and cytostatic medicines with code numbers 18 01 08*, 18 02 07* and 20 01 31* are classified as "absolute entry" hazardous waste. All other pharmaceutical waste is classified as non-hazardous by European regulations. Greek regulations (CMD, 2012) consider cytostatic waste as hazardous medical waste with only toxic character.

There are several papers dealing with healthcare waste generation in Greece (Voudrias and Graikos, 2014; Komilis *et al.,* 2017; Komilis and Katsafaros, 2011; Kalogiannidou *et al.,* 2018; Graikos *et al.,* 2010). However, there is very limited information regarding pharmaceutical waste production by hospitals and people's homes and how much of active ingredients are contained in such waste (Becker, 2010; Voudrias *et al.,* 2012). Although there are many papers on infectious waste generation by hospitals and limited information on general pharmaceutical waste, no such information exists for cytostatic waste, which is a special category of pharmaceutical waste. This information, however, is necessary for the design and costing of management systems (collection, transport, treatment and disposal, e.g., Mantzaras and Voudrias, 2017) for cytostatic waste. The choice of treatment technology is also important. For example, the proper treatment technology for cytostatic waste is incineration, whereas both incineration and disinfection can be used for infectious waste (Voudrias, 2016). Quantification of cytostatic waste generation is also important for health and safety reasons and for assessing their environmental impact, when they are released in the environment.

To address the above research needs, this work was designed with an overall objective to determine the composition and production rates of cytostatic pharmaceutical waste produced by Theagenion Cancer Treatment Hospital (TCTH) of Thessaloniki, in Greece. Specific objectives were: (1) To determine the daily production (g/d) and unit production rates (g/patient/d, g/bed/d) for different cytostatic pharmaceutical waste categories by individual wards and the hospital as a whole. (2) To determine the daily production of residual amounts of different cytostatic pharmaceutical waste categories by individual wards and the hospital as a whole. (3) To determine possible correlations between daily production and daily number of patients, so that measurements can be used in a predictive fashion.

Theagenion is the cancer treatment hospital of Thessaloniki, which is the capital of the Region of Central Macedonia and the second largest city in Greece. The population of the metropolitan area of Thessaloniki is 1.012.297 people, according to the 2011 census (Hellenic Statistical Authority, 2017).

2. Materials and methods

2.1. Activity at Theagenion Cancer Treatment Hospital

The following wards/departments of Theagenion Cancer Treatment Hospital participated in this study and are the main cytostatic pharmaceutical waste generators (Kermenidou *et al.,* 2013): Interdisciplinary day clinic (43 beds), Pathology (69 beds), Hematology (23 beds) and Gastroenterology (22 beds). At the time of the study, the hospital had 357 beds for patient care. The average daily number of patients in these wards during the study period was 195±87 and the total number of patients over the same period was 8194.

2.2. Cytostatic pharmaceutical waste at TCTH

For the purpose of this study, the cytostatic pharmaceutical waste was classified in three types (Voudrias *et al.,* 2012; Kermenidou *et al.,* 2013): (1) vial waste, (2) syringe waste and (3) waste from intravenous therapy (IVs). Vial waste comprised the initial glass or plastic containers containing residual amounts of cytostatic pharmaceuticals in liquid or solid form. They were labeled by drug manufacturers with the name and initial quantity of cytostatic pharmaceutical. Syringe waste comprised used syringes without needles, with residual amounts of cytostatic pharmaceuticals in liquid form. Waste syringes from each ward/department were lumped together, because they could not be sorted, according to their cytostatic drug content. IV waste comprised plastic bags containing the cytostatic pharmaceutical solution and connected to IV lines, which administer the cytostatic drug to the patient's vein. The end points of IV lines contained blood drops and were excluded from the measurement. IVs containing non-cytostatic drugs were not considered in this study. All these categories are classified as hazardous medical waste under Greek Regulations (CMD, 2012).

2.3. Collection of cytostatic pharmaceutical waste

Vial and syringe waste were collected from May to September 2011 for 6 working weeks, one week per month randomly selected during the sampling month. Source separation of cytostatic pharmaceutical waste was conducted by nurses at each ward/department. They were instructed and supervised by the authors of this study to ensure that the waste was collected in the right

red bag, pre-labeled with a self-adhesive label having the date and origin of the waste (Becker, 2010; Voudrias *et al.,* 2012). Specifically, vials containing residual amounts of pharmaceuticals and used syringes with no needles, following medical praxis, and expired medicine were placed in the red plastic bags. Plastic bags were collected at the end of the working shift on each collection day and were transported by waste collection crew using wheeled containers in a storage room and were weighed (Kermenidou *et al.,* 2013). Because of partial collection of IV waste by mistake during the above collection period, it was decided to repeat IV collection over a 4-week period. IV waste was placed in red plastic bags and was transferred to the storage room.

2.4. Separation, weighing and recording

A procedure similar to the one described in Voudrias *et al.* (2012) was followed. Vial waste separation was conducted according to the name of their cytostatic content in the label (e.g., Epibra, a known cytostatic antibiotic). Then, vials containing the same cytostatic drug were weighed together and recorded in Microsoft Excel spreadsheets. In addition, the residual amounts contained in each vial were visually estimated (without weighing) based on the original content, summed and recorded.

All syringes were grouped together, regardless of their content. Their separation according to their drug content was impossible, because they were not labeled. Assessment of their residual amounts was more accurate than in the vials, because of syringe graduation. A similar procedure was followed for IVs containing cytostatic waste. That is all IV waste was reported together, either as total waste or total residual amount. The residual amount was determined by subtracting the container weight from the total IV waste.

All sorted vial cytostatic waste was classified in five major categories, according to Anatomical Therapeutic Classification system (WHO, 2012) and National Drug Organization of Greece (EOF, 2018): Alkylating agents, antimetabolites, cytotoxic antibiotics, Vinca alkaloids and other antineoplastic drugs. The latter category contains some kinds of cytostatic pharmaceuticals found in smaller quantities and not on daily basis, including biological modifiers, podophyllotoxins, supportive care drugs and syringes.

Along with the amount of waste collected, the number of beds in each ward and the number of patients entering the respective wards on the particular sampling days was also recorded in excel spreadsheets. Therefore, the term "patient" refers to everybody entering the hospital for medical examination, regardless if he was then hospitalized or not. The daily number of patients and the number of beds were used to calculate unit production rates in g/patient/d and g/bed/d, respectively. In wards/departments with beds, the unit production rate g/patient/d is equivalent to g/occupied bed/d. More details are presented in Voudrias *et al.* (2012).

Personal protective equipment, such as a white laboratory coat, a paper mask, glasses, surgeon's foot covers and double pair of plastic gloves, were used by the first author involved in waste separation and weighing.

2.5. Statistical analysis of data

Using appropriate equations (Mandalidis *et al.,* 2018; Komilis and Katsafaros, 2011; Komilis *et al.,* 2017; Kalogiannidou *et al.,* 2018), waste weight data were used to calculate the following waste production indices: (1) the daily production by each ward/department in g/d, (2) the average total daily production by the hospital in g/d, (3) the average patient-based unit production rate in g/patient/d and (4) the average bed-based unit production rate in g/bed/d. Similar equations were used when production rates were calculated with respect to a cytostatic waste category, e.g., Vinca alkaloids. Correlations between daily production and the respective number of patients were developed. The Anderson-Darling test was used to check for normality of the g/d, g/patient/d and g/bed/d data. The p values of the test larger than the designated level of significance (α = 0.05) indicate normal distribution of the data.

3. Results and discussion

3.1. Production of vial waste

Presentation of the Results and Discussion is structured according to Voudrias *et al.* (2012). The total amount of vial cytostatic pharmaceutical waste produced by wards/departments, which was collected and analyzed over the 42 days of the study, was 369 kg and the total number of patients producing the waste was 8194. Table 1 presents the average daily number of patients and the average daily production (g/d) of vial waste. The columns present the average daily production of the five waste categories, whereas the last column shows the total amount of vial cytostatic waste produced by TCTH. Numbers in parentheses, both in Tables and the text, are the respective standard deviation values. The total vial waste production by TCTH was 8782 (4883) g/d. Figure 1 presents the daily variation of total vial cytostatic waste production by wards/departments of TCTH. Obviously, the daily weekend production was much smaller than the weekday production. This was due to the much smaller average number of patients (64±10 patients/d) treated on weekends, compared to the respective weekday average (247±26 patients/d).

The high standard deviations computed for some wards/departments were attributed to considerable variation in the daily number of patients. In addition, some patients could leave the hospital without having consumed cytostatic drugs there.

The largest producer of total vial cytostatic waste was the interdisciplinary day clinic with average daily production of 5168 (1719) g/d (42% of total production), followed by pathology with 3465 (1819) g/d (39.5% of total). The smallest producer was gastroenterology with 749 (500) g/d (8.5%) (Table 1).

Comparing the cytostatic waste categories, alkylating agents were found in the largest quantity with 3807 (2176) g/d (43.4% of total), followed by "other" antineoplastic drugs with 2096 (1352) g/d (23.9%), the antimetabolites with 1939 (1172) g/d (22.1%), the cytostatic antibiotics with 898 (655) g/d (10.2%) and Vinca alkaloids with 42 (35) g/d (0.5%) (Table 1).

Table 1. Average daily production of vial cytostatic waste by TCTH. Number in parentheses are standard deviations

Ward/department	Average daily number of patients		Alkylating agents		Antimetabolites		Cytotoxic antibiotics		Vinca alkaloids		Other antineoplastic drugs		Total	
	patients/d	%	g/d	%	g/d	%	g/d	%	g/d	%	g/d	%	g/d	%
Inderdisciplinary day clinic	132 (18)	48.2	2096 (864)	39.4	1031 (537)	38.0	1015 (455)	80.8	34 (24)	57.6	993 (401)	33.8	**5168 (1719)**	42.0
Pathology	60 (18)	30.9	1627 (868)	42.7	728 (591)	37.5	111 (90)	12.3	8(14)	18.0	992 (719)	47.3	**3465 (1819)**	39.5
Hematology	21 (4)	10.6	442 (292)	11.6	164 (156)	8.5	58 (79)	6.4	10 (17)	24.4	203 (155)	9.7	**877 (317)**	10.0
Gastroenterology	20 (7)	10.3	241 (247)	6.3	312 (231)	16	5(15)	0.5	0	0	192 (190)	9.2	**749 (500)**	8.5
Total	**195 (87)**	**100**	**3807 (2176)**	**100**	**1939 (1172)**	**100**	**898 (655)**	**100**	**42 (35)**	**100**	**2096 (1352)**	**100**	**8782 (4883)**	**100**
%			**43.4**		**22.1**		**10.2**		**0.5**		**23.9**			**100**

Table 2. Average daily production of residual amounts of cytostatic pharmaceuticals (visually estimated) in vial waste by TCTH. Numbers in parentheses are standard deviations

Ward/department	Alkylating agents		Antimetabolites		Cytotoxic antibiotics		Vinca alkaloids		Other antineoplastic drugs		Total	
	g/d	%	g/d	%	g/d	%	g/d	%	g/d	%	g/d	%
Inderdisciplinary day clinic	24(30)	48.9	13(14)	49	14(13)	72.2	0.8(1)	61.7	14(11)	28.8	**67(57)**	**45.3**
Pathology	12(10)	35.4	6(5)	31.2	3(3.5)	19.3	0.2(0.8)	22.2	18(14)	50.1	**39(26)**	**37.4**
Hematology	3.8(4.5)	10.7	1.4(1.3)	7.2	1(1.2)	6.7	0.2(0.5)	16.0	3(3)	8.2	**9.2(6)**	**8.7**
Gastroenterology	1.8(2.3)	5.0	2.4(2)	12.6	0.3(0.9)	1.8	-	-	5(7)	12.9	**9(9.2)**	**8.6**
Total	**35(36)**	**100**	**19(17)**	**100**	**14.2(13.7)**	**100**	**1(1.4)**	**100**	**36(24)**	**100**	**105(79)**	**100**
%	**33.4**		**18.0**		**13.5**		**0.9**		**34.2**			**100**

Table 3. Average unit production rates of vial cytostatic pharmaceutical waste by TCTH. Numbers in parentheses are standard deviations

Ward/department	Alkylating agents		Antimetabolites		Cytotoxic antibiotics		Vinca alkaloids		Other antineoplastic drugs		Total	
	g/patient/d	g/bed/d	g/patient/d	g/bed/d	g/patient/d	g/bed/d	g/patient/d	g/bed/d	g/patient/d	g/bed/d	g/patient/d	g/bed/d
Inderdisciplinary day clinic	16(5)	No beds	8(4)	No beds	8(3)	No beds	0.3(0.2)	No beds	7(3)	No beds	**38(10)**	**No beds**
Pathology	26(9)	24(13)	11(8)	11(9)	1.7(1.3)	1.6(1.3)	0.1(0.19)	0.1(0.2)	14.9(9.7)	14.4(10.4)	**54(19)**	**50(26)**
Hematology	21(13)	19(13)	8.3(8)	7.1(6.8)	3(4.4)	2.5(3.5)	0.5(0.8)	0.4(0.7)	9.6 (7.3)	8.8(6.7)	**42(14)**	**38(14)**
Gastroenterology	11 (11)	11(11)	15(10)	14(10)	0.2(0.8)	0.2(0.7)	0	0	9.3(9.7)	8.7(8.6)	**35(22)**	**34(23)**
Total	**18(5)**	**33(19)**	**9(4)**	**17(10)**	**4(2)**	**8(6)**	**0.2(0.2)**	**0.4(0.3)**	**10(4)**	**18(12)**	**41(11)**	**77(46)**

The largest producer of alkylating agents was the interdisciplinary day clinic with average daily production of 2096 (864) g/d (39.4% of total production of alkylating agents), followed by pathology with 1627 (868) g/d (42.7%). Although the daily production was smaller than interdisciplinary day clinic, the % with respect to total amount produced was higher, because the interdisciplinary day clinic operated only on week days, i.e., 30 days total, while pathology operated 7 days per week, i.e., 42 days total. The smallest producer was gastroenterology with 241 (247) g/d (Table 1).

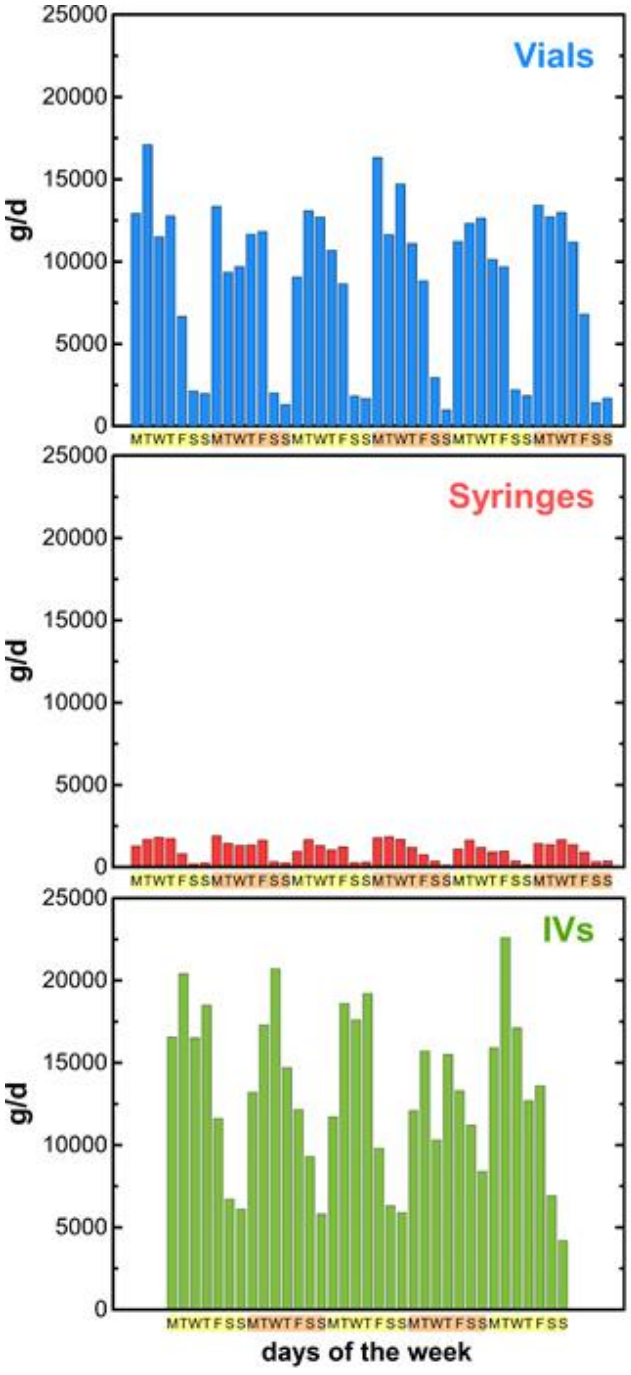

Figure 1. Daily production of cytostatic pharmaceutical waste produced by TCTH

The interdisciplinary day clinic was also the largest producer for antimetabolites with average daily production of 1031 (537) g/d (38%), cytostatic antibiotics with 1015 (455) g/d (80.8%), Vinca alkaloids with 34 (24) g/d (57.6%) and other antineoplastic drugs with 993 (401) g/d (33.8%).

The residual amounts of cytostatic pharmaceutical waste contained in the vials were visually estimated and the results are presented in Table 2. The total estimated residual amount over the 42 days of the study was 4.4 kg and the total average daily production was 105 (79) g/d. The largest producer was again the interdisciplinary day clinic with 67 (57) g/d (45.3% of total). "Other" antineoplastic drugs were found in the largest production rate of 36 (24) g/d (34.2% of total).

Table 3 shows two different trends in unit production rates (Becker, 2010; Voudrias *et al.,* 2012): (1) For each single ward/department, g/patient/d > g/bed/d, because bed occupancy was lower than 100%. Only when the number of patients equals the number of beds, the difference in unit production rates is zero. (2) For each cytostatic pharmaceutical waste category and the overall vial waste produced by the hospital, g/patient/d < g/bed/d. This happened because interdisciplinary day clinic had beds only for daily care of a large number of patients. Thus, the average daily number of patients for the whole hospital was higher than the total number of beds (195 (87) patients/d > 114 beds of the hospital), resulting in patient-based unit production rates to be lower than the respective bed-based unit production rates. Unit production rates as g/bed/d for interdisciplinary day clinic were not calculated.

The total average unit production rates of vial cytostatic waste produced by TCTH were 41 (11) g/patient/d and 77 (46) g/bed/d (Table 3). The respective rates measured for total vial pharmaceutical waste produced by a Greek General Hospital in Xanthi (Voudrias *et al.,* 2012) were 6.38 (1.60) g/patient/d and 12.6 (2.61) g/bed/d, i.e., several times lower. Pathology with 54 (19) g/patient/d and 50 (26) g/bed/d had the highest production rates while gastroenterology with 35 (22) g/patient/d and 34 (23) g/bed/d had the lowest. Comparing the cytostatic waste categories, alkylating agents with 18 (5) g/patient/d and 33 (19) g/bed/d had the highest production rates, while Vinca alkaloids with 0.2 (0.2) g/patient/d and 0.4 (0.3) g/bed/d had the lowest.

Figure 2 presents the correlation between daily production of vial cytostatic waste and the respective number of patients, for the 42 days of measurements. The R^2 = 0.913 value indicates that the correlation is statistically significant at α = 0.05 and sample size = 42. The gap in the data was due to differences between weekdays and weekends in waste production and the number of patients. The regression equation (Figure 2 and Table 4) is valid within the range of daily number of patients 49 < x < 293. The *F* value calculated was very large (*F* = 417.52) and it holds 417.52>>4*F**(1,40df) = (4)(4.08) = 16.32. Therefore, the regression equation y = 53.90 x -1735 (Figure 2 and Table 4) has some practical

predictive value at α = 0.05 (Berthouex and Brown, 2002, p. 341). The calculated *F* value is the ratio of regression mean square to residual mean square, while *F** is the critical value of the *F* distribution (Berthouex and Brown, 2002, pp. 303, 341). The 95% confidence intervals of parameters **a** and **b** do not contain zero, indicating that **a** and **b** are statistically significant at α = 0.05. The residuals of the linear model follow a normal distribution with a zero mean, which is a necessary condition for the model (Berthouex and Brown, 2002, p. 290).

3.2. Production of syringe waste

The total amount of syringe cytostatic waste produced by TCTH was 43.2 kg over the 42 days of the study. Table 5 presents the average daily production of syringe cytostatic waste by the wards/departments of TCTH. Since syringe waste could not be separated by drug category, it is reported as total amount produced by each ward/department. The overall average syringe waste produced by the hospital was 1029 (573) g/d. Figure 1 presents the daily production of syringe waste and compares this with vial and IV production.

Table 4. Linear regression equations between daily production (y in g/d) and the respective number of patients (x in patients/d)

Waste type	Regression equation y = ax + b	Standard error of intercept "a"	Standard error of intercept "b"	R^2	Statistical significance at α = 0.05
Vial waste	y = 53.91x-1735	2.64	562	0.913	Yes
Syringe waste	y = 5.384x	0.187	0	0.798	Yes
IV waste	y = 44.92x+4753	4.86	1007	0.721	Yes

Table 5. Average daily production of total syringe cytostatic waste, of residual amounts and average unit production rates by wards/departments of TCTH. Numbers in parentheses are standard deviations

Ward/department	Total syringe waste		Residual amount		Average unit production rate	
	g/d	% of total	g/d	% of total	g/patient/d	g/bed/d
Inderdisciplinary day clinic	624(220)	43.3	0.7(2)	15.1	5(2)	No beds
Pathology	348(223)	33.8	2(4)	58.1	5.4(2.8)	5(3.2)
Hematology	140(55)	13.6	0.3(2)	7.6	7(3)	6(2)
Gastroenterology	96(73)	9.3	1(2)	19.2	4.6(3)	4(3)
Total	**1029(573)**	**100**	**3(6)**	**100**	**5(1.5)**	**9(5)**

Table 6. Average daily production of total IV cytostatic waste, of residual amounts and average unit production rates by wards/departments of TCTH. Numbers in parentheses are standard deviations

Ward/department	Total IV waste		Residual amount		Average unit production rate	
	g/d	% of total	g/d	% of total	g/patient/d	g/bed/d
Inderdisciplinary day clinic	5392 (2920)	36.9	4692 (2920)	39.7	39 (15)	No beds
Pathology	4511 (1375)	30.8	3811 (1375)	32.2	98 (67)	65 (20)
Hematology	2346 (1184)	16.0	1646 (1184)	13.9	179 (131)	102 (51)
Gastroenterology	2380 (934)	16.3	1680 (934)	14.2	143 (67)	108 (42)
Total	**13089 (4919)**	**100**	**10489 (4673)**	**100**	**94 (63)**	**115 (43)**

Table 7. Average daily production of total cytostatic waste, of residual amounts and average unit production rates by wards/departments of TCTH. Numbers in parentheses are standard deviations

Ward/department	Total cytostatic waste		Residual amount		Average unit production rate	
	g/d	%	g/d	%	g/patient/d	g/bed/d
Inderdisciplinary day clinic	11184 (3396)	42.9	4760 (2921)	39.8	82 (18)	No beds
Pathology	8324 (2291)	31.9	3852 (1375)	32.2	157 (70)	120 (33)
Hematology	3363 (1227)	12.9	1656 (1184)	13.8	228 (132)	146 (53)
Gastroenterology	3225 (1062)	12.4	1690 (934)	14.1	183 (71)	146 (48)
Total	**22900 (6955)**	**100**	**10597 (4673)**	**100**	**140 (64)**	**201 (61)**

The largest producer was interdisciplinary day clinic with 624 (220) g/d (43.3% of total production), followed by pathology with 348 (223) g/d (33.8%) and hematology with 140 (55) g/d (13.6%). Gastroenterology was the smallest syringe waste producer with 96(73) g/d (9.3%).

Table 5 also shows the residual amounts of cytostatic drugs contained in the waste syringes, which were visually

estimated. The total residual amount over the 42 days of the study was 145.5 g, with average total daily production of 3(6) g/d. Pathology was the largest producer (58.1%), followed by gastroenterology (19.2%).

The average unit production rates of total syringe cytostatic waste produced by TCTH were 5(1.5) g/patient/d and 9(5) g/bed/d (Table 5). The respective rates measured for total syringe pharmaceutical waste produced by a Greek General Hospital (Xanthi General Hospital) (Voudrias *et al.,* 2012) were 1.4(0.4) g/patient/d and 2.8(0.8) g/bed/d, i.e., several times lower. The largest producer was hematology with 7(3) g/patient/d and 6(2) g/bed/d and the smallest was gastroenterology with 4.6(3) g/patient/d and 4(3) g/bed/d.

Figure 3 shows the correlation between daily production of syringe cytostatic waste and the respective number of patients, over the 42 days of measurements. The R^2 = 0.798 value indicates that the correlation is statistically significant at α = 0.05 and sample size = 42. The gap in the data was explained as in Figure 2. The regression equation (Figure 3 and Table 4) is valid within the range of daily number of patients 49< x <293. The *F* value calculated was very large (*F* = 833.02) and it holds 833.02>>4*F**(1,40df) = (4)(4.08) = 16.32. Therefore, the regression equation y = 5.384x (Figure 3 and Table 4) has some practical predictive value at α = 0.05 (Berthouex and Brown, 2002, p. 341). The slope of the line (5.384) approaches the average production rate of 5(1.5) g/patient/d (Table 5). The 95% confidence interval of parameter **a** (slope) does not contain zero, indicating that **a** is statistically significant at α = 0.05. The residuals of the linear model follow a normal distribution with a zero mean, which is a necessary condition for the model (Berthouex and Brown, 2002, p. 290).

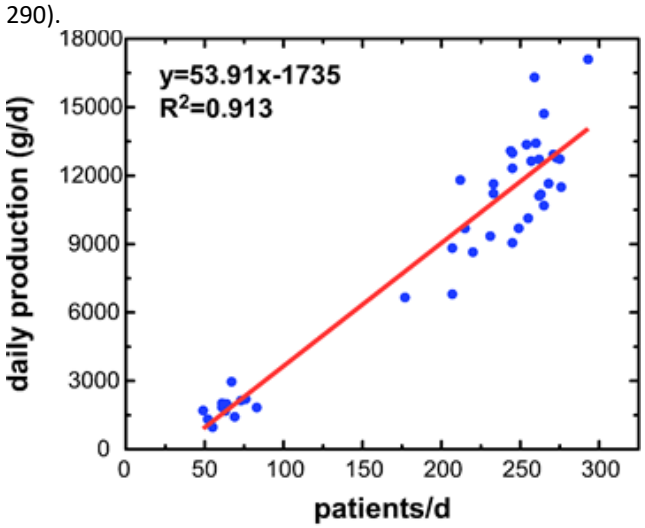

Figure 2. Linear correlation between total daily production of vial cytostatic waste and respective daily number of patients for TCTH

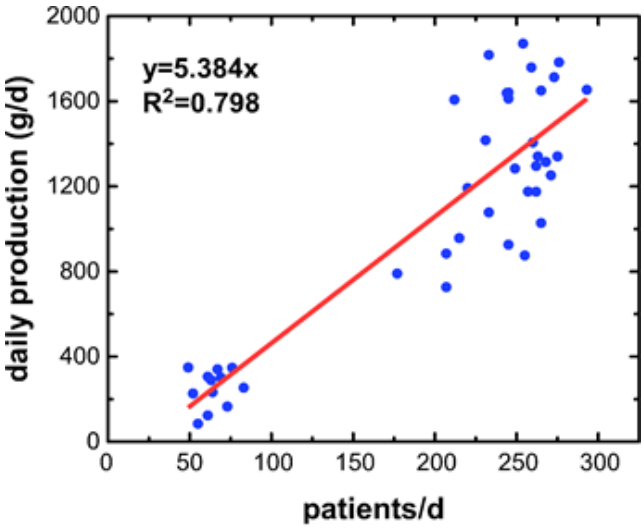

Figure 3 Linear correlation between total daily production of syringe cytostatic waste and respective daily number of patients for TCTH

3.3. Production of IV waste

The total amount of IV cytostatic waste produced by TCTH during this study was 367 kg. Table 6 presents the average daily production, the residual amounts and the average unit production rates of total IV cytostatic waste by the wards/departments of TCTH. Since IV waste could not be separated by drug category, it is reported as total amount produced by each ward/department. The residual amount was calculated by subtracting the weight of the plastic container. The overall average IV waste produced by the hospital was 13089 (4919) g/d. Figure 1 presents the daily production of IV waste and compares this with vial and syringe production. The largest producer was interdisciplinary day clinic with 5392 (2920) g/d (36.9% of total production), followed by pathology with 4511 (1375) g/d (30.8%).

The average unit production rates of total IV cytostatic waste produced by TCTH were 94 (63) g/patient/d and 115 (43) g/bed/d (Table 6). The larger bed-based than patient-based unit production rate was attributed to the smaller number of total beds than total patients, since the interdisciplinary day clinic with the largest number of patients had no beds. The respective rates measured for total IV pharmaceutical waste produced by a Greek General Hospital (Xanthi General Hospital) (Voudrias *et al.,* 2012) were 4.6 (3) g/patient/d and 9.2 (5.9) g/bed/d, i.e., more than an order of magnitude lower. The largest producer was hematology with 179 (131) g/patient/d and 102 (51) g/bed/d.

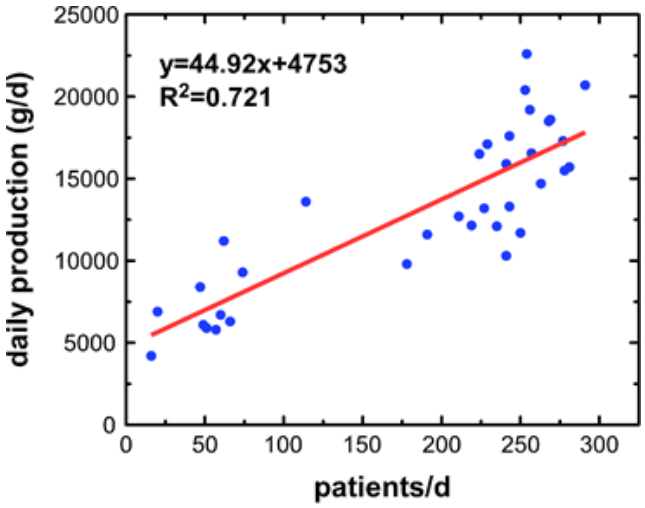

Figure 4. Linear correlation between total daily production of IV cytostatic waste and respective daily number of patients for TCTH

Figure 4 shows the correlation between daily production of IV cytostatic waste and the respective number of patients, over the 35 days of measurements. The R^2 = 0.721 value indicates the correlation is statistically significant at α = 0.05 and sample size = 35. The gap in the data was again explained as in Figure 2. The regression equation (Figure 4 and Table 4) is valid within the range of daily number of patients 16 < x < 291. The F value calculated was F = 85.3 and it holds 85.3>4F^*(1,35df) = (4)(4.17) = 16.68. Therefore, the regression equation y = 44.92x+4753 (Figure 4 and Table 4) has some practical predictive value at α = 0.05 (Berthouex and Brown, 2002, p. 341). The 95% confidence intervals of parameters **a** and **b** do not contain zero, indicating that **a** and **b** are statistically significant at α = 0.05.

3.4. Total production of cytostatic waste

The total amount of cytostatic waste produced by TCTH equals the sum of vial, syringe and IV waste. The overall cytostatic waste generation by TCTH was 22900 (6955) g/d. IV waste was produced in the largest quantity with 13089 (4919) g/d (57.2% of total), followed by vial waste with 8782(4883) g/d (38.3%) and syringe waste with 1029 (573) g/d (4.5%) (Tables 1, 5 and 6). The main cytostatic waste producer was interdisciplinary day clinic with 11184 (3396) g/d (42.9%), followed by pathology with 8324 (2291) g/d (31.9%) (Table 7).

The overall production of residual amounts by wards/departments of TCTH was 10597 (4673) g/d. IV waste was produced in the largest quantity with 10489 (4673) g/d (98.98% of total), followed by vial waste with 105 (79) g/d (0.99%) and syringe waste with 3 (6) g/d (0.03%) (Tables 2, 5 and 6). Interdisciplinary day clinic was the main producer with 4760 (2921) g/d (39.8%), followed by pathology with 3852 (1375) g/d (32.2%) (Table 7).

Based on the results of the Anderson-Darling test, the original total daily production data (g/d) for vial and syringe waste did not follow a normal distribution (p<0.005). This was caused by outliers corresponding to the much smaller waste generation (g/d) over the weekend (Figure 1). In contrast, total IV daily production data were normally distributed (p = 0.529>0.05). A similar distribution was observed for the respective total unit production rates in g/bed/d, since they were calculated by dividing daily production by the same number of beds of the hospital. When total daily production was normalized with respect to the daily number of patients (i.e., g/patient/d), total vial waste (p = 0.776) and total syringe waste (p = 0.288) followed normal distribution. In contrast, total IV waste did not follow normal distribution (p<0.05), because of the presence of two outliers. However, outliers were not removed from the analysis and from the results reported in this paper. In most cases, waste production by individual wards/departments followed normal distribution.

The average unit production rates of total cytostatic waste by TCTH were 140 (64) g/patient/d and 201 (61) g/bed/d (Table 7). An average production rate of 404±59% g/bed/d of hazardous medical waste from four Greek cancer treatment hospitals was reported by Komilis *et al.* (2012). This value is larger than the respective value of 201 (61) g/bed/d measured in this work, because it includes all types of hazardous health care waste produced by these hospitals (i.e., infectious, mixed and toxic). The respective rates measured for total pharmaceutical waste produced by a Greek General Hospital (Xanthi General Hospital) (Voudrias *et al.,* 2012) were 12.4 (3.9) g/patient/d and 24.6 (7.5) g/bed/d. The much higher rates measured for the cancer hospital indicate the much higher demand for anti-cancer drugs required for fighting cancer. The largest producer was hematology with 228 (132) g/patient/d, followed by gastroenterology with 157 (70) g/patient/d. Comparing the three waste categories, IVs were measured in the highest production rates of 94 (63) g/patient/d and 115 (43) g/bed/d, followed by vial waste with 41 (11) g/patient/d and 77 (46) g/bed/d.

The regression equations of Table 4 were used to calculate daily production of cytostatic waste as a function of daily number of patients. Total production was calculated by addition of the vial, syringe and IV waste for the same daily number of patients. The resulting equation was y = 104.2x+3018. This can be used by the hospital administrator for planning purposes.

4. Conclusions

This work has successfully addressed the research needs, accomplished the objectives stated in the Introduction and produced the following conclusions:

- Total cytostatic pharmaceutical waste produced by TCTH was classified in three categories, vial waste comprising 38.3%, syringe waste with 4.5% and IV waste with 57.2% of the total.
- The average unit production rates of total cytostatic pharmaceutical waste produced by TCTH were 140 (64) g/patient/d and 201 (61) g/bed/d.
- Comparing the cytostatic vial waste categories, alkylating agents were found with the largest unit

production rates of 18 (5) g/patient/d and 33 (19) g/bed/d, followed by "other" antineoplastic drugs with 10 (4) g/patient/d and 18 (12) g/bed/d, by antimetabolites with 9 (4) g/patient/d and 17 (10) g/bed/d, by cytotoxic antibiotics with 4 (2) g/patient/d and 8 (6) g/bed/d and Vinca alkaloids with 0.2 (0.2) g/patient/d and 0.4 (0.3) g/bed/d.

- Statistically significant linear correlations were established between daily production and the respective number of patients for vial, syringe and IV waste.
- Unit production rates of cytostatic pharmaceutical waste were much higher compared to non-cytostatic pharmaceutical waste produced by another Greek General Hospital. This indicates the much higher demand for anti-cancer drugs required for fighting cancer, compared to other pharmaceuticals.
- The results of the study are necessary for the design and costing of management systems for cytostatic pharmaceutical waste, for assessing their environmental impact and for health and safety considerations.

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