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Dose intensity of adjuvant CMF chemotherapy program for breast cancer

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Introduction. Adjuvant therapy has an established position in breast cancer treatment. CMF multidrug program is one of the most frequently used. Dose intensity (DI), relative dose intensity (RDI) and average relative dose intensity (aRPI) of CMF reginect has bees assed..
Material and methods. Between October 1994 and January 2000, 110 women with breast cancer received adjuvant chemotherapy according to the CMF regimen. To assess the intensity of treatment we applied the criteria for multidrug programmes suggested by Hryniuk et al., i.e. the definitions and models of dose intensity (DI), relative dose intensity (RDI), and the average relative dose intensity (aRDI).
Results. The values of dose intensity for individual drugs, as well as the intensity of treatment for the CMF program, were presented in 5 value intervals, where 0.7 was assumed to be the lowest effective value. For the CMF regimen aRDI was: not less than 1.0 in 16 patients (15%), 0.9-1.0 in 44 patients (40%), 0.8-0.9 in 23 patients (21%), 0.7-0.8 in 17 patients (15%), and less than 0.7 in 10 patients (9%). The intensity of treatment was affected by dose reductions of the individual drugs, delays in drug administration and the co-existance of reductions and delays resulting in a majority of cases from I and II degree hematologic toxicity, and in one case – from neutropenic fever. In seven cases, aRDI was affected by earlier termination of treatment resulting from the toxicity of chemotherapy. Follow-up varied between 1 and 54 months, (mean 24 months). An attempt of the analysis of disease free survival and overall survivals was undertaken in the assessed group.
Conclusions. No differences in the relative intensities of doses for individual cytostatics were noted. No corelation between the dose intensity of CMF and both the disease free interval and overall survival in the investigated group was found.

Intensywność leczenia uzupełniajacego programem CMF u chorych na raka piersi po radykalnym leczeniu chirurgicznym

Wstęp. Rak piersi jest nowotworem, w którym leczenie uzupełniające ma ustaloną pozycję. Jednym z najczęściej stosowanych programów wielolekowych w leczeniu uzupełniającym jest program CMF. Oceniono intensywność dawki (DI), względną intensywność dawki (RDI) i średnią intensywność dawki (aRDI) dla programu CMF.
Materiał i metody. W okresie od października 1994 r. do stycznia 2000 r. leczono uzupełniająco programem CMF 110 kobiet chorych na raka piersi. Do oceny intensywności leczenia wykorzystano definicję i wzór intensywności dawki (DI) oraz względnej intensywności dawki (RDI), a także średniej względnej intensywności dawki dla programu wielolekowego (aRDI) wg Hryniuka.
Wyniki. Wartości intensywności dawek dla poszczególnych cytostatyków, a także intensywności leczenia dla programu CMF, przedstawiono w 5 przedziałach wartości, uznając za najmniejszą skuteczną wartość 0,7. Dla programu CMF aRDI wynosiła: co najmniej 1,0 u 16 pacjentek (15%), pomiędzy 0,9 a 1,0 u 44 pacjentek (40%), pomiędzy 0,8 a 0,9 u 23 pacjentek (21%), pomiędzy 0,7 a 0,8 u 17 pacjentek (15,%), poniżej 0,7 u 10 pacjentek (9%). Na intensywność leczenia miały wpływ redukcje dawek poszczególnych cytostatyków, wchodzących w skład programu, odroczenia podawania leków, a także współistnienie redukcji i odroczeń, wynikające w większości przypadków z toksyczności hematologicznej w stopniu I i II, w 1 przypadku z gorączki neutropenicznej. U 7 chorych wpływ na aRDI miało wcześniejsze zakończenie leczenia związane z toksycznością

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chemioterapii. Czas obserwacji wyniósł od 1 do 54 miesięcy, średnio 24 miesiące. Podjęto próbę analizy przeżyć bezobjawowych i całkowitych w ocenianej grupie chorych.
Wnioski. Nie zanotowano różnic we względnych intensywnościach dawek dla poszczególnych cytostatyków. W badanej grupie chorych nie wykazano zależności pomiędzy intensywnością leczenia programem CMF, a długością czasu bezobjawowego przeżycia i całkowitego przeżycia.

Key words: breast cancer, adjuvant treatment, CMF program, dose intensity
Słowa kluczowe: rak sutka, leczenie uzupełniające, program CMF, intensywność dawki

Introduction

Adjuvant therapy has established itself firmly in the treatment of breast cancer. The results of adjuvant therapy are evaluated according to: overall survival, disease free survival, annual decrease of recurrences and death risk. Randomised trials proved that multiple drug chemotherapy prolongs overall survival and disease free survival. These results were further confirmed in a meta-analysis [1]. Best effects of adjuvant polychemotherapy are observed in premenopausal, node positive women, or in women aged below 50 years [1, 2]. One of the most widely used treatment regimens is a three drug protocol, which includes cyclophosphamide, methotrexate and 5--fluorouracil (referred to as CMF), introduced by Bonadonna et al. in the early seventies [3]. A correlation between it's dose intensity and the results of therapy was proved. Decrease of the total cytostatic dose of the CMF regimen to the values below 0.85 deteriorates 3-year disease free survival rate [3, 4]. The reasons of decreasing the dose intensity below 0.7, i.e. below what is accepted to be the lowest effective dose [3, 5], and an analysis of overall survival and disease free survival are presented in this study.

Material and methods

One hundred and ten randomly chosen women, treated in the Department of Breast Cancer and Reconstructive Surgery by adjuvant CMF therapy between October 1994 and January 2000, were analysed retrospectively. The age of the patients ranged between 31 and 69 years (mean – 47). Ninety five patients were premenopausal, and 15 – postmenopausal. All patients underwent primary radical treatment: modified radical mastectomy was performed in 99 cases while 11 cases had breast conserving therapy (BCT). Adjuvant chemotherapy was initiated not later than 6 weeks after surgery. In cases of BCT, radiotherapy was given simultaneously with the CMF. Chemotherapy was followed by radiotherapy in three patients after mastectomy who had metastases in more than three lymph nodes.

Patient characteristics are presented in Table I.

The oral-intravenous CMF regimen was as follows:

cyclophosphamide (CTX)	100 mg/m^2/day	orally	day 1 to 14
methotrexate (MTX)	40 mg/m^2/day	i.v.	day 1 and 8
5-fluorouracil (5-Fu)	600 mg/m^2/day	i.v.	day 1 and 14

This regimen was repeated every 28 days.

Six cycles in 6 months are given. The guidelines for treatment modificatios are presented in Table II. Until the year 1998, the dose reduction was carried out according to the number of leukocytes according to WHO criteria, including the cases of grade 1 haematologic toxicity. At present, dose reductions are performed according to the real number of neutrophiles. The end of treatment was indicated in cases of grade 3 or 4 toxicity. Haematopoetic factors were not administered preventively according to the WHO criteria.

Treatment intensity was calculated according to the definitions and principles given by Hryniuk [4, 6, 7]. Dose Intensity (DI) is the dose of a cytostatic drug given in a time unit. Dose intensity is calculated in mg/m^2/week, independently of the treatment regimen and of the route of administration.

Relative Dose Intensity (RDI) is the dose of a cytostatic drug given in a time unit in mg/m^2/week correlated with a standard drug dose (sDI).

The sDI in the CMF regimen were as follows: 350 mg/m^2/week for CTX, 20 mg/m^2/week for MTX and 300 mg/m^2/week for 5-Fu [5].

The Average Relative Dose Intensity (aRDI) for multiple drug regimen is calculated as follows:

$$aRDI_{CMF} = (RDI_{CTX} + RDI_{MTX} + RDI_{5\text{-}Fu})\ [3].$$

Dose Intensity for each of the three drugs was calculated for each patient according to these guidelines.

Tab I. Characteristics of 110 patients receiving adjuvant CMF chemotherapy in years 1994 to 2000

Characteristics	Number of patients
Premenopausal	95
Postmenopausal	15
Mastectomy	99
BCT	11
Postoperative radiotherapy	
after mastectomy (and chemotherapy)	3
after BCT (simultaneously with chemotherapy)	11
Histopathological type of cancer:	
invasive ductal carcinoma	88
Grade	
G1	4
G2	39
G3	39
no data	6
lobular carcinoma	12
other	10
Histopathological status of axillary lymph nodes: number of metastatic lymph nodes:	
0	24
1-3	81
>3	5
3 patients had less then 10 axillary lymph nodes removed	
Receptors E/Pg	
unknown	56
both positive	20
one positive	13
both negative	21

Results

The dose intensity for each drug and for the entire CMF regimen was presented in five value ranges. The lowest effective value was estimated at the level of 0,7 [3, 5]. The percentage circular graph is used to illustrate these results.

The relative dose intensity (RDI) for cyclophosphamide (CTX) was not less than 1.0 in 12 patients (15%), 0.9-1.0 in 44 patients (40%), 0.8-0.9 in 23 patients (21%), 0.7-0.8 in 17 patients (15%) and below 0.7 in 10 patients (9%). (see Fig. 1).

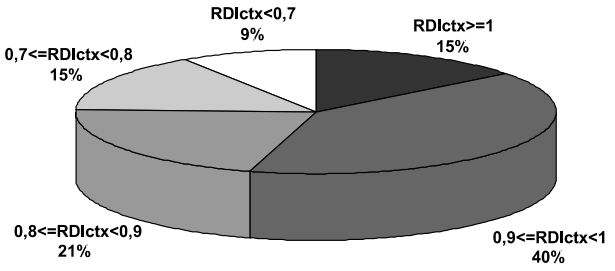

Fig. 1. Relative dose intensity of CTX

The relative dose intensity (RDI) for methotrexate (MTX) was not less than 1.0 in 17 patients (15%), 0.9-1.0 in 49 patients (45%), 0.8-0.9 in 21 patients (19%), 0.7-0.8 in 15 patients (14%), and below 0.7 in 8 patients (7%) (see Fig. 2).

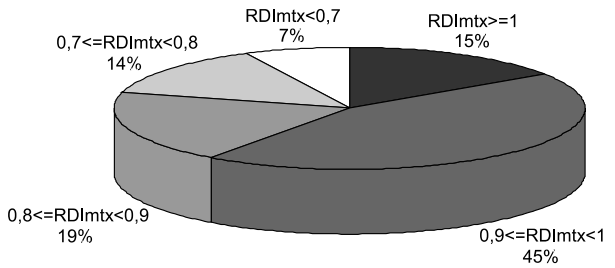

Fig. 2. Relative dose intensity of MTX

The relative dose intensity (RDI) for 5-fluorouracyl (5-Fu) was not less than 1.0 in 14 patients (13%), 0.9--1.0 in 52 patients (47%), 0.8-0.9 in 20 patients (18%), 0.7--0.8 in 15 patients (14%) and below 0.7 in 9 patients (8%) (see Fig. 3).

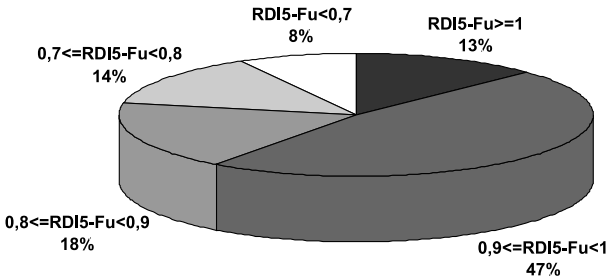

Fig. 3. Relative dose intensity of 5-Fu

The average relative dose intensity for the entire CMF regimen was: not less than 1.0 in 14 patients (13%),

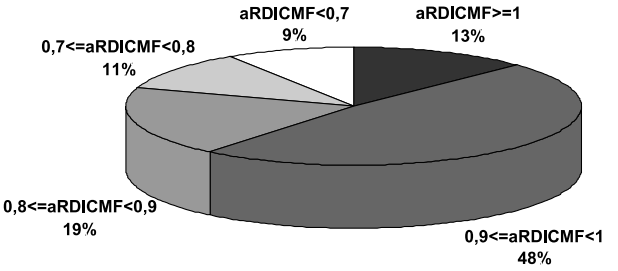

Fig. 4. Averange relative dose intensity of CMF

0.9-1.0 in 21 patients (19%), 0.8-0.9 in 12 patients (11%), 0.7-0.8 in 12 patients (11%), and below 0.7 in 10 patients (9%) (see Fig. 4).

The patients were divided into three groups according to the CMF average relative dose intensity. Group 1 had an average relative dose intensity below 0.7 (n = 10 pts. i.e. 9%), group 2, – an aRDI of 0.7 – 0.9, (33 pts i.e. 30%) and group 3, aRDI of not less than 0.9, (67 patients i.e. 52%). We assumed an average relative dose above 0.7 to be effective. This result was calculated for patients from group 1 and 2, and was achieved by 100 patients (82%).

The dose intensity was influenced by: dose reductions, delays in drug administration and a co-existence of both reductions and delays arising from treatment modifications resulting from haematological toxicity Table II.

Tab. II. Diagram of cytostatic dose reduction

Before year 1998		
Leucocyte count in mm^3	Platelet count in mm^3	Percentage of original dose
≥4000	≥100000	100% (full dose)
3000-3999	75000-99000	75%
2000-2999	50000-74000	50%
<2000	<50000	0%
Since 1998		
Granulocyte count in mm^3	Platelet count in mm^3	Percentage of original dose
At least 1500	75000-100000	100% (full dose)
Below 1500	<75000	0%

Hematological toxicity was usually observed as a recurrent and chronic decrease of white blood cell count, grade 1 or 2. The dose of cytostatic drugs was decreased in 215 cycles; in 24 cycles the therapy was delayed (see Tab. III and Tab. IV). In one patient, neutropoenic fever was observed and the treatment was terminated earlier than it was planned, after only four cycles. In seven patients, the treatment was modified because of a sole grade 1 or 2 decrease in platelet count, while in five cases this decrease coexisted with a decrease in the neutrophil count. Only in three of these patients did aRDI fall below 0,7.

Tab. III. Frequency and reasons of cytostatic dose reduction

Number of cycle	Leucopenia grade I or II	Leucopenia grade III	Leucopenia grade IV	Febrile neutropenia	Thrombocytopenia grade I or II	Both leucopenia and thrombocytopenia	Other
I	8	0	0	0	0	0	0
II	28	0	0	0	0	0	1 (stomatitis II°)
III	34	0	0	0	3	1	0
IV	43	2	0	0	3	1	2 (cystitis, stomatitis II°)
V	48	2	0	0	1	0	0
VI	54	6	0	1	0	2	0

Tab. IV. Reasons and frequency of treatment delay (at least 7 days)

Number of cycle	Leucopenia	Thrombocytopenia	Both leucopenia and thrombocytopenia	Infections without neutropenia	Febrile neutropenia	Others*
I	0	0	0	0	0	1
II	2	0	0	3	0	1
III	2	0	1	2	0	3 (1x hiperbilirubinemia)
IV	6	0	0	2	0	5
V	6	0	0	7	0	4 (1 x significant hypertension)
VI	8	0	0	4	1	1

* except specifications – patients reasons

The average relative dose intensity fell below 0.7 in 10 patient. Seven of them terminated therapy earlier because of serious infections, digestive tract haemorrhage, cardiotoxicity, haematological toxicity and unacceptable heavy vomiting (see Tab. V).

Rounding of the doses of each drug in every cycle did not influence the average dose intensity.

Follow-up varied between one month and 54 months, (mean – 24.1 months). A minimum two-year overall survival beginning with the completion of chemotherapy was achieved in 75 patients, 66 of whom remain free of disease. Progression of the disease was seen in nine patients. The disease free interval in these patients varied between 12 and 41 months (mean 27.4 months). Four patients had visceral metastases and also four had soft tissue and bone lesions, while in one case both visceral and soft tissue lesions were found.

Five patients had ductal carcinoma (2-G2, 3-G-3), two – lobular carcinoma and two – mixed ductal and lobular type. All these patients presented axillary lymph node metastases. In one patient aRDI was below 0.7, in the others it was not less than 0.85 (see Tab. VI).

The follow-up period beginning from the termination of chemotherapy does not exceed two years for 35

Tab. V. Reasons for earlier cessation of treatment in patients with aRDI <0.7

aRDI value	Number of administered cycles	Reasons cessation of treatment
0.37	IIIa	Pneumonia with hospitalisation
0.48	IIa (next – IV cycle of CMF iv)	Non-acceptable nausea and vomiting grade II
0.51	IVa	Myocardial ischemia in ECG requiring hospitalisation
0.54	IIb (next – VI cycle of CMF iv)	Returning and prolonged leucopenia and thrombocytopenia
0.61	IV	Leucopenia grade III with postradiation reaction and fever more then 39°C during radiotherapy given simultaneously with chemotherapy
0.62	IV	Mycosis and bleeding from digestive tract, anemia
0.67	IV	Hypertension (300/170 mmHg) requiring hospitalisation

Tab. VI. Analysis of relapses in patients with overall survival of at least 2 years

aRDI value	Time to progression in months	Metastatic site	Hormonal status	Histopathology	Receptors E/Pg
0.65	26	liver	premenopausal	ductal ca G2 MBR2 pT1cN1 w – 1/17	E – positive Pg – positive
0.85	12	scar	premenopausal	mixed ca pTxN1 w – 1/12	E – positive Pg – positive
0.89	41	bones	premenopausal	lobular ca pT2N1bi w – 1/12	unknown
0.90	24	liver, supraclavicular lymph nodes	premenopausal	ductal ca G3 MBR3 pT2, pN-brak w – 10/16	unknown
0.91	39	lymph nodes supraclavicular bilateral	premenopausal	ductal ca G2 MBR3 pT2N1 w – 1/15	E – negative Pg – positive
0.92	28	lungs	postmenopausal	ductal ca G3 pT2N1 w – 4/4	E – negative Pg – negative
0.92	35	bones	premenopausal	lobular ca pT3N1 w – 1/13	unknown
0.97	24	scar	premenopausal	mixed ca pT2N1 w – 1/12	unknown
1.00	18	liver	premenopausal	ductal ca G3 MBR3 pT2N1 w – 2/14	unknown

w – number of metastatic axillary lymph nodes / number of examinated lymph nodes
E – estrogen receptor
Pg – progestagen receptor

patients. Four patients in this group died because of metastatic disease. One of them had the first relapse in the viscera, two – in soft tissues and the remaining one both in the viscera and in soft tissues. The disease free survival in these patients ranged between 3 and 14 months (mean 8.3 months). All these patients died because of cancer progression during the first 24 months after relapse. Three of them had positive lymph nodes and grade 3 ductal carcinoma aRDI was below 0.7, in one patient aRDI was at least 0.83 in the remaining three (see Tab. VII).

Discussion

The role of dose intensity in adjuvant treatment is widely discussed. In a prospective randomised trial carried out in the seventies on 386 patients Bonadonna and Valagusa proved that 12 cycles of adjuvant CMF statistically significantly prolonged the disease free survival period, as compared to the group of women who were treated only surgically [2].

In a second consecutive randomised trial the same investigators compared the efficacy of 12 cycles of CMF versus 6 cycles of the same treatment. In a group of 458 patients there was no statistically significant difference between the shorter and longer therapy [8]. A retrospective analysis of these two trials in 1981 proved that the total dose of all cytostatics plays a crucial part in prolonging the disease free interval and the total survival [3]. In that report the authors analysed the real doses of all administered drugs and compared them with the doses, which should be given according to the regimen pattern. The patients were divided into three sub-groups. The first sub-group consisted of patients who received more than 85% of the calculated dose; the second of those, receiving between 84% and 65% of the calculated dose, and the third sub-group of those, receiving less than 65% of the planned dose. The first sub-group consisted of 17% of patients, the second – of 50% and the third – of 33%. The treatment had to be modified because of haematological toxicity in 32% of cases, while in 33% of cases it was terminated due to the stomatitis and other causes. The treatment was terminated aforetime in 8% of patients. Nevertheless 17% of patients received a dose, which equalled or exceeded 85% of the dose acknowledged as full. There was a correlation between the total administered dose and the risk of treatment failure. Among the patients who received more than 85% of the

Tab. VII. Analysis of relapses in patients with follow-up shorter then 24 months

aRDI value	Time to progression in months	Metastatic site	Hormonal status	Histopathology	Receptor status
0.68	14*	Liver, abdominal lymph nodes	premenopausal	ductal ca G3 MBR5 pT2N1 w – 1/12	E – negative Pg – negative
0.83	3*	lungs	postmenopausal	ductal ca G3 MBR5 pTN-brak w – 0/14	E – negative Pg – negative
0.91	9*	scar	premenopausal	medullar ca pT2N1 w – 2/17	unknown
0.92	7*	scar	premenopausal	ductal ca G3 MBR4 pT2N1 w – 1/16	unknown

* – death in time shorter then 24 months after end of treatment
w – number of metastatic axillary lymph nodes / number of examinated lymph nodes
E – estrogen receptor
Pg – progestagen receptor

planned dose, 77% had a 5-year disease free survival. In patients who received 84% – 65% of the calculated dose and in those who received less than 65% of the calculated dose these values were 56% and 48% respectively. The same 5-year disease free interval was observed in 45% of patients from the control group, who did not receive CMF. The overall survival was related to the total received dose of CMF treatment. Overall 5-year survival was achieved also in 80% of patients from subgroup 1; 67% of patients from subgroup 2 and 67% of patients in subgroup 3. In the control group 5-year overall survival reached 66%. Adjuvant CMF was most effective in premenopausal women with less than 4 lymph node metastases. After this initiatory study the possible relation between the intensity of the treatment and the survival period was widely investigated. In a study performed by Colleoni et al. on a group of 1350 patients treated with adjuvant CMF for 6 months the patients were divided into three subgroups according to the total given dose of the drugs. Subgroup 1 received over 85% of the calculated dose; subgroup 2 – 65% to 85%; subgroup 3 less than 65%. The longest disease – free period and overall survival time was achieved among patients from subgroup 2. Adjuvant chemotherapy was less effective when the actual administered dose was reduced by more than 35%. Haematologic toxicity was the most frequent reason for drug dose reduction [5]. It was postulated that the better outcome observed in the second subgroup might arise from drug dose reduction carried out according to individual tolerance and causing more effective drug absorption. It is not fully understood why the results of therapy were worse in subgroup 1, than in subgroup 2. One of the most feasible explanations was that the frequent occurrence of relapse might be related to worse prognosis of patients in this subgroup [3, 5]. Hryniuk and others conducted a retrospective study and suggested, that there is a correlation between the pattern of treatment and its intensity. They were the first to present such terms as „dose intensity" and „relative dose intensity". Hryniuk et al. showed, a correlation between the dose intensity and the 3-year disease free survival in premenopausal and postmenopausal patients with positive lymph nodes [4].

In our study an average relative dose intensity of at least 0.7 was achieved in 91% of patients treated with adjuvant CMF. During the mean 24 month follow-up period we did not discover any correlation between the average dose intensity and both the disease free survival and the overall survival. The most frequent reason for drug dose reduction was haematological toxicity. In five patients the average dose intensity felt below 0.7 due to of heamatologic toxicity and in another group of five patients because of other toxicities connected with the CMF treatment. We observed recurrences in 13 patients. The average dose intensity exceeded 0.8 in 11 of them. Treatment failure was connected with bad prognosis in these patients. Our studies are preliminary and longer observation appears to be necessary.

Conclusions

1. There was no relation between the CMF dose intensity and both the disease-free interval and overall survival.
2. There was no difference between the relative dose intensity of each single drug used in the CMF regiment.
3. There were no unnecessary dose modifications.

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