Resumen

Objetivo: Conocer las intensidades de dosis relativas (IDR) en pacientes con cáncer de mama y tratamiento quimioterápico. Determinar el número de pacientes donde la IDR fue < 85% de la programada y posible causa.

Método: Estudio retrospectivo, periodo de selección de 4 meses. Se registraron: edad, superficie corporal, protocolo administrado, intención de tratamiento, frecuencia de administración de ciclos, número de tratamientos citostáticos recibidos anteriormente y administración de filgrastim. Se calculó la IDR media por paciente y protocolo.

Resultados: Se analizaron 110 pacientes, edad media 55,4 años (intervalo: 31-84), superficie corporal media 1,7 m² (1,3-2.4). La IDR media global fue 91,0% (DE 10,7). Del 93,8% (10,6), 95,8% (6,3) y 81,9% (18,5) en neoadyuvancia, adyuvancia y tratamiento paliativo, respectivamente. El 20% de pacientes no alcanzó una IDR ≥ 85% de la programada, IDR media 69,5% (3,29). Un retraso en la administración de quimioterapia igual o superior a 7 días ocurrió en 45,4% de los casos, IDR media 80,7% (16,0). En los episodios donde se disminuyó la dosis por toxicidad la IDR fue 75,6% (13,6). Se obtuvieron relaciones inversas significativas de la edad (p = 0,02) y línea de tratamiento (p = 0,03) con la IDR. En un 36,8% la reducción de dosis fue por neutropenia, recibiendo filgrastim el 52,9%.

Conclusiones: La mayoría de pacientes recibió una IDR adecuada. La edad, tratamientos anteriores e intención de tratamiento fueron las variables que más afectaron a la dosis recibida. El retraso en la administración del ciclo fue la actuación más frecuente para minimizar la toxicidad y que menos afectó al tratamiento.


Summary

Objective: To know relative dose intensity (RDI) in patients with breast cancer treated with chemotherapy. To determine the number of patients where RDI was < 85% of that programmed and the possible cause.

Method: Retrospective study, four-month selection period. The following were recorded: age, body surface, protocol applied, intention of treatment, frequency of administration of cycles, number of cytostatic treatments previously received and filgrastim administration. The average RDI per patient and protocol was calculated.

Results: 110 patients were analysed, the average age of them being 55.4 years (interval: 31-84), average body surface 1.7 m² (1.3-2.4). Overall average RDI was 91.0% (SD 10.7). 93.8% (10.6), 95.8% (6.3) and 81.9% (18.5) in neoadjuvant, adjuvant and palliative treatments, respectively. 20% of the patients did not reach a RDI ≥ 85% of that programmed, average RDI 69.5% (3.29). A delay in the administration of chemotherapy equal or greater than seven days occurred in 45.4% of the cases, average RDI 80.7% (16.0). In the episodes where the dose was reduced because of toxicity, the RDI was 75.6% (13.6). Significant inverse ratios were obtained with age (p = 0.02) and line of treatment (p = 0.03) with the RDI. In 36.8%, dose reduction was caused by neutropenia; 52.9% received filgrastim.

Conclusions: Most patients received the appropriate RDI. Age, previous treatments and intention of treatment were the variables with the greatest impact on the dose received. The delay in administering the cycle was the most frequent act minimising the toxicity and which least affected the treatment.

INTRODUCTION

Breast cancer is considered the most frequent neoplasm among women worldwide, followed by colorectal and stomach cancer. Invasive breast neoplasia accounts for around 35% of all cancers suffered by women in our environment, with a gross rate of 105.6 new cases per 100,000 women in 2001. At world level, the rate of invasive breast cancer in women is lower, specifically 19.1%, due to a higher incidence of uterine and lung cancer in this group.

According to data from the Agencia de Evaluación de Tecnología e Investigación Médicas de Cataluña [Agency for the Evaluation of Medical Technology and Research of Catalonia], one in every 19 women may suffer from breast cancer before the age of 74, at an average age of 62. The principal risk factors associated are early menarche, nulliparity, late menopause, family history and patient’s age. Between 5 and 10% of hereditary breast cancers are associated with mutations of the BRCA1 and BRCA2 genes. Relative survival at five years has significantly increased from 66.7% between 1985 and 1989 to 75.9% between 1990-1994; however, it is still the main cause of death by cancer among women. Gross mortality rate was also progressively increasing until 1991-1992, when it was established at 34.1%, but it has since decreased annually by 2.2%. Mortality due to this type of cancer have increased among postmenopausal women, although the figures show an overall fall in mortality, attributable to different causes, among which there is an improvement in early diagnosis thanks to the introduction to the public screening campaign, together with the application of new therapeutic strategies.

Overall survival (OS) and disease-free survival (DFS) are related to multiple variables, some relating to chemotherapeutic treatment, such as number and introduction of prior received protocols, as well as others relating to the clinical situation of the patient. The risk of developing remote metastases increases with the presence of metastases in lymph glands, tumour size and loss of histological differentiation. Other prognostic factors include high levels of uPA and PAI1 proteins, low expression of oestrogen and progesterone receptors and amplification of the gene ERBB2. Finally, in the subgroup of patients without ganglionic infiltration, genetic expression profiles have been described that predict the risk of metastasis, although these require prospective assessment.

In the various pharmacokinetic and pharmacodynamic studies, a lineal increase in cytotoxicity has been observed according to the dose administered, while the probability of the appearance of resistant tumours decreases. Consequently, one of the parameters considered useful for predicting the efficacy of a cytostatic treatment is dose intensity (DI). Moreover, both for breast cancer and other types of tumours, DI is defined as the amount of cytostatic administered by body surface (BS) and by unit of time (mg/m²/week). Some studies show that obtaining a relative dose intensity (RDI) equal to or greater than 85% of that programmed is a positive predictive factor for OS and DFS, both for adjuvant chemotherapy and metastatic breast cancer treatment.

By contrast, the decrease of RDI below 85% programmed, regardless of the cause, can be considered a clinically relevant negative predictive factor in the evolution of the disease. In this respect, it is estimated that more than 60% of the patients receiving chemotherapy as adjuvant treatment for breast cancer undergo reductions in the programmed DI. Specifically, between 21 and 30% of the patients received less than 85% of some of the most frequent protocols.

Furthermore, neutropenia is one of the most common adverse effects responsible for decreasing dose intensity, appearing in 29% of patients undergoing adjuvant chemotherapy treatments. 11% of patients suffering from neutropenia receive less than 85% of the programmed DI. 50% of the patients presenting neutropenia manifest it during the first two cycles of chemotherapy.

The objectives of this study are to calculate the RDI received in the group of patients selected, classifying the results according to the intention of treatment and chemotherapy protocol used. Secondly, to determine the groups in which the RDI obtained was below 85% and identify and analyse the possible causes and associated factors.

METHOD

A retrospective study carried out using the pharmacotherapeutic follow-up database and preparing cytostatic medications for oncohaematological patients. In the analysis, there were included all the patients with primary breast tumours receiving complete chemotherapy for this indication (Table I) between the months of November 2004 and February 2005. All the cycles corresponding to active treatment during the study period were compiled and analysed. Age, clinical condition, chemotherapy protocol administered, intention of treatment (neoadjuvant, adjuvant or palliative), number of different cytostatic protocols received earlier, frequency of administration of the chemotherapeutic cycle (weekly, every 14, 21 or 28 days, or days 1, 2 and 3 every 21 days), dose reductions, delays in the administration of chemotherapy and reasons for the possible administration of granulocyte colony-stimulating factors (G-CSF).

Dose intensity of every cytostatic administered was calculated (DIadm) based on the method of Hryniuk et al., total dose administered (mg/m²) divided by the number of weeks of treatment, starting on the first administration and ending in the week of the final administration. These were divided by the theoretical dose intensity according to the protocol administered (DI), thus obtaining the relative dose intensity (RDI). When administering more than one cytostatic per protocol, the average RDI was calculated from the RDI of each separate cytostatic.
The reasons causing RDI below 85% were registered, according to the decrease in the initial dose, delay in the administration of chemotherapy equal to or longer than seven days, or others. The cycle during which incidence was produce was also recorded, as well as whether the patient presented neutropenia.

The statistical treatment was carried out using the SPSS 10.0. package. To describe the clinical and demographic variables, average and standard deviations were used, and for qualitative ones, the percentage of cases. The comparison among groups of continuous variables with a normal distribution was carried out using the t-Student test in the case of two categories, and ANOVA for more than two categories per variable. In cases where conditions were not suitable for its application, the corresponding non-parametric tests were used (U by Mann-Whitney and H by Kruskall-Wallis). When significant data were obtained, post-hoc contrasts were applied using the Scheffé test. The relationship between qualitative variables was analysed using contingency tables, verifying the probability using the $\chi^2$ test and contingency coefficient. Pearson lineal correlation ratio was applied to the quantitative variables, as well as lineal regression in the case of good correlation. We considered the different tests statistically significant when we obtained probability values equal to or lower than 0.05.

**RESULTS**

For the study period, 116 patients were identified, six of whom were rejected because of lack of data; therefore, the definite sample comprised 110 patients. The study population is described in table II. The most frequently prescribed chemotherapy protocols for breast cancer treatment were FAC, docetaxel and FEC. Table III describes the distributions of the different protocols.
administered together with their average RDI and average age of the patients receiving them.

The average RDI administered to a total of 110 patients studied was 91% (SD 10.7). A progressive and statistically significant decrease in overall RDI was observed when the number of different cytostatic combinations previously received increased (p = 0.03). In palliative treatments, from third-line treatment, overall RDI decreased to 70.6% (SD 19.5).

Average RDI according to the intention of treatment was 93.3% (SD 10.6) in neoadjuvant treatments, from 95.8% (SD 6.4) in adjuvant ones and 81.9% (SD 18.5) in the palliative. Average difference in RDI between palliative and adjuvant treatments was 13.9%, characterising RDI with adjuvant intention always being over 93% in all patients.

The carboplatin/etoposide chemotherapeutic protocol with palliative intention was characterised by having the lowest value of all average RDI calculated [69.6% (SD 17.6)]. The protocol with an adjuvant intention FAC had the highest average RDI maximum value [96.8% (SD 7.1)]. These differences between average RDI of the two protocols described above were statistically significant (p = 0.02).

The number of patients receiving a RDI lower than 85% of that programmed was 22 (20%) of the 110 patients included. These had an average RDI of 69.5% (SD 3.3). According to the intention of treatment, the average RDI in this group of patients was 80.7% (SD 1.8) in adjuvant, 72.8% (SD 3.1) in neoadjuvant, and 64.9% (SD 6.2) in palliative treatments. The average age of the group that experienced a serious reduction in the RDI of their treatments (≥15%) was 60.3 (SD 13.1) years, significantly higher than that of the rest of the patients [54.4 (SD 12.2) years] (p = 0.02). The causes for the decrease in RDI were: reduction in the initial doses prescribed (8 of 22 patients) and a delay in the administration of treatment equal to or longer than 7 days (10 of 22 patients). In the first option, an average RDI of 75.6% (SD 13.6) was obtained, while delaying administration produced a higher average RDI, of 80.7% (SD 16.0). The four remaining patients had already started the treatment at lower doses than those described in the appropriate protocols.

Neutropenia led to a decrease in the RDI in 36.8% of the patients. Average RDI of patients suffering from neutropenia was 75.1% (SD 14.1). G-CSF (filgrastim) was administered to 34 patients (30.9%), 16 of whom (47.1%) received it as primary prophylaxis. Average RDI obtained in patients receiving filgrastim as treatment was 87.8% (SD 15.5), while in those who received it as prophylaxis, it was 96.9% (SD 5.2).

**Table II. Description of study population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Average (interval) or percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.4 (31-84)</td>
</tr>
<tr>
<td>Body surface (m²)</td>
<td>1.7 (1.3-2.4)</td>
</tr>
<tr>
<td>Patients receiving chemotherapy for the first time</td>
<td>59.1%</td>
</tr>
<tr>
<td>Patients receiving treatment with neoadjuvant intention</td>
<td>16.4%</td>
</tr>
<tr>
<td>Patients receiving treatment with palliative intention</td>
<td>27.2%</td>
</tr>
</tbody>
</table>

**Table III. Distribution of protocols with their RDI average ages**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Number</th>
<th>%</th>
<th>RDI (Average ± SD)</th>
<th>Age (Average ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCE</td>
<td>26</td>
<td>23.6</td>
<td>96.8 ± 7.2</td>
<td>51.7 ± 11.6</td>
</tr>
<tr>
<td>Docetaxel every 21 d</td>
<td>15</td>
<td>13.6</td>
<td>95.4 ± 14.0</td>
<td>50.3 ± 10.9</td>
</tr>
<tr>
<td>FEC</td>
<td>12</td>
<td>10.9</td>
<td>93.2 ± 5.8</td>
<td>54.0 ± 14.2</td>
</tr>
<tr>
<td>AC</td>
<td>9</td>
<td>8.2</td>
<td>84.5 ± 33.5</td>
<td>60.3 ± 10.2</td>
</tr>
<tr>
<td>CMF D (1.8) every 28 d</td>
<td>8</td>
<td>7.3</td>
<td>94.4 ± 4.5</td>
<td>61.0 ± 10.8</td>
</tr>
<tr>
<td>ET</td>
<td>7</td>
<td>6.4</td>
<td>94.8 ± 6.9</td>
<td>54.0 ± 11.3</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>6</td>
<td>5.4</td>
<td>72.9 ± 20.0</td>
<td>62.2 ± 10.9</td>
</tr>
<tr>
<td>EC</td>
<td>5</td>
<td>4.5</td>
<td>95.8 ± 5.2</td>
<td>56.2 ± 11.6</td>
</tr>
<tr>
<td>Doxorubicin liposomal every 28 d</td>
<td>5</td>
<td>4.5</td>
<td>85.8 ± 15.0</td>
<td>68.6 ± 13.9</td>
</tr>
<tr>
<td>Carboplatin/etoposide</td>
<td>4</td>
<td>3.6</td>
<td>69.8 ± 17.6</td>
<td>49.0 ± 9.8</td>
</tr>
<tr>
<td>Doxorubicin every 21 d</td>
<td>3</td>
<td>2.7</td>
<td>85.8 ± 9.6</td>
<td>54.0 ± 4.4</td>
</tr>
<tr>
<td>Trastuzumab every 21 d</td>
<td>3</td>
<td>2.7</td>
<td>82.4 ± 28</td>
<td>63.3 ± 11.7</td>
</tr>
<tr>
<td>Inappropriate</td>
<td>2</td>
<td>1.8</td>
<td>/</td>
<td>42.5 ± 14.8</td>
</tr>
<tr>
<td>Gemcitabine/vinoreline</td>
<td>2</td>
<td>1.8</td>
<td>83.9 ± 11.9</td>
<td>75.0 ± 7.0</td>
</tr>
<tr>
<td>CMF every 21 d</td>
<td>1</td>
<td>0.9</td>
<td>96.6 ± 0.0</td>
<td>54.0 ± 0.0</td>
</tr>
<tr>
<td>Paclitaxel/trastuzumab</td>
<td>1</td>
<td>0.9</td>
<td>82.8 ± 0.0</td>
<td>33.0 ± 0.0</td>
</tr>
<tr>
<td>FEC 75</td>
<td>1</td>
<td>0.9</td>
<td>94.0 ± 0.0</td>
<td>70.0 ± 0.0</td>
</tr>
</tbody>
</table>

^Standard deviation; ^Initial dose differ from the established protocols.

**DISCUSSION**

The calculation of RDI, as the main study variable and predictive factor of the efficacy of chemotherapeutic treatment, was made considering that the contribution of the different cytostatics on the OS and DFS was the same. In this way, and as the studies consulted in this respect, the concept of total dose intensity (TDI) was not used, since it would involve the calculation of individualised values by class of cytostatic.

Most patients (80%) received an appropriate RDI, within the limits appearing in the majority of works evaluating the impact of dose reduction on the evolution of breast cancer. Although there is a larger number of studies in patients following an adjuvant treatment, dose intensity is also an important variable to be taken into account to evaluate the effectiveness of breast cancer treatments with a palliative intention.

In the overall results presented in this study, we have included patients treated with adjuvant, neoadjuvant and palliative intentions of treatment. In this way, if we consider only the patients with adjuvant and neoadjuvant intentions of treatment, the average RDI increases to 90% and the percentage of patients with an important reduction of RDI decreases to a mere 10%. The value of average RDI is similar to that obtained in the class of studies mentioned above; however, the number of patients not receiving a sufficient dose intensity is lower when con-
Considering only adjuvant and neoadjuvant treatments. These differences are attributable to, among others, the type of calculation applied to obtain the RDI, the high percentage of patients receiving G-CSF and sample size, much smaller if compared with other types of multi-centre studies.

RDI were lower when increasing the number of different cytostatic prior treatments. The inverse relationship was observed in patients under palliative treatment and especially from the third chemotherapy protocol.

The progressive increase in the age of the patients affected the RDI received, as did the number of different cytostatic combinations received earlier. As no significant relationship between the age and the number of chemotherapeutic combinations received earlier exists in the results obtained in our study, these two variables can be proposed as negative factors for the prognosis for RDI received.

Delays in the administration of the chemotherapeutic cycle equal to or longer than seven days were the most frequently used procedure to minimise the toxicity. This option was the one least affecting the study principal variable, in contrast to the reduction of cytostatic doses, a procedure with greater repercussions on the final RDI.

The RDI reached in this study by adjuvant treatments were very satisfactory. The RDI in the treatment of metastatic disease were slightly lower, a decrease related to the variables of age and number of different cytostatic combinations received earlier. The concept of dose intensity, applied to chemotherapeutic treatments received in daily practice by our patients is a specific indicator that allows us to quantify the quality of the healthcare process and to assess the need for possible concomitant measures and planning of pharmacotherapeutic protocols. The aim will be to affect dose intensity received to the smallest degree possible, taking into account the different factors capable of influencing this, such as chemotherapeutic doses reduction due to toxicity, the factor with the greatest impact on the decrease of RDI.

RDI enables us to effectively compare the results obtained in our normal clinical practice with the different research works published. Supervising the doses actually received by the patients together with the concomitant measures to favour their administration is a multidisciplinary task and its main objective will be to improve the efficacy of the chemotherapeutic treatment of cancer.

References


