Phase II study of an oral combination of doxifluridine, prednimustine and idarubicin (FUPRIDA) for first line treatment of advanced breast cancer

P. Alberto
Division d’Onco-Hématologie, Hôpital Cantonal Universitaire, Geneva, Switzerland

Summary

Background: An oral combination chemotherapy for breast cancer may be of advantage for many patients, if its activity is equivalent to that of i.v. treatments. The bioavailability of oral idarubicin and of oral doxifluridin allows for their use in an oral 3 drug regimen.

Patients and methods: Idarubicin 29 mg/m² was given on day 1, doxifluridine 1500 mg and prednimustine 60 mg were given daily for 10–14 days (7 days/m²) in 17 patients with advanced breast cancer. Cycles (1 to 18) were repeated every 4 weeks or delayed if required by toxic effects.

Results: Nine responses were observed with durations ranging from 2 to 16 months. Responding lesions were the primary tumor, or skin, liver and bone metastases. WHO grade 3–4 toxic effects included leukopenia (7 patients), diarrhea and emesis (2 and 1 patient). There were no toxic deaths.

Conclusions: If our results are confirmed, this oral 3-drug-combination is a safe and effective treatment that may improve the quality of lives of breast cancer patients with poor venous access.

Key words: breast cancer, doxifluridine, idarubicin, prednimustine

Introduction

An intravenous combination of cyclophosphamide, doxorubicin and fluorouracil (CAF or FAC) is frequently used for adjuvant or advanced-stage treatment of breast cancer. In advanced stages, CAF is slightly superior to CMF (cyclophosphamide, methotrexate and fluorouracil) in terms of tumor response rate [1, 2] and possibly also in terms of survival time [1].

Oral antitumor chemotherapy plays a positive role in the quality of the lives of cancer patients [3]. This could be the case for adjuvant treatment of breast cancer, or for home therapy in patients with advanced stages. Oral prednimustine, an alkylating agent with a good digestive tolerance and a low risk of alopecia, is active in breast cancer [4]. New oral analogues of doxorubicin and of fluorouracil have been developed. Oral idarubicin has shown some activity in breast cancer [5]. Intravenous doxifluridine is active in breast cancer, but its use is limited by neurotoxicity and cardiotoxicity [6] that were not observed with the oral form [7].

The objective of this open, non-randomized trial, was to investigate the tolerance and antitumor activity of an oral first-line combination of doxifluridine, prednimustine and idarubicin in advanced breast cancer patients.

Patients and methods

A total of 19 patients with histologically confirmed advanced breast cancer and measurable lesions entered this trial. Venous access was poor or the patients wanted to avoid intravenous treatment. Blood counts, liver function tests and serum creatinine were within normal range. No patient had digestive dysfunction. In a preliminary step, the 2 first patients received doses corresponding to 60% of full doses. They are not included in the evaluation of toxicity and response. The median age of the 17 evaluable patients is 63 years (45–69). The median time from diagnosis to study treatment is 50 months (23–204). Sixteen patients had had breast surgery, 11 post-surgical radiotherapy, 12 hormonal treatment, 6 adjuvant chemotherapy which terminated six or more months before entry and none had had palliative chemotherapy. Measurable tumor lesions were the primary tumor (1), local recurrence (4), regional lymph nodes (2), or lesions in bone (9), liver (7), lung (5), skin (4) and pleura (2). The study started in October 1987 and was interrupted in March 1989 because oral doxifluridine was no longer available. Two further patients could be treated until February 1992. The study was then closed due to the lack of drug supply.

Treatment cycles were repeated every 4 weeks. Blood counts were repeated before each new cycle and the treatment was delayed in instances of prolonged toxicity. Idarubicin was obtained from Farmitalia Carlo Erba, Switzerland, as 5 mg, 10 mg and 25 mg capsules. A single dose of 29 mg/m² was given on day 1 only, adjusted to the nearest 5 mg level. Doxifluridine was obtained from Farmitalia Carlo Erba, Switzerland, as 500 mg ampules of drinking solution. Commercially available 20 mg prednimustine tablets were used. As the available formulations of doxifluridine and prednimustine were not adequate for a precise adjustment of the daily dose to the body surface, all patients were given 500 mg doxifluridine and 20 mg prednimustine 3 times daily, starting on day 2. The number of treatment days was adjusted to the body surface from 10 to 14 days, or 7 days/m². With this treatment schedule, the dose intensity [8] is 7.25 mg/m²/week for idarubicin, 105 mg/m²/week for prednimustine and 2625 mg/m²/week for doxifluridine. The individual dose intensities relative to the protocol regimen were calculated for every patient from day 1 to the first day of the last treatment cycle, which was not included in the calculation. One patient received one cycle only and is excluded from the study of dose intensity.
Results

Nine patients experienced objective tumor responses. The response duration ranged from 2 to 16 months, with a median of 6 months. Responding lesions were the primary tumor with massive skin involvement (1 patient), and secondary lesions in the skin (3 patients), the liver (4 patients) and bones (3 patients).

Patients received a median of 4 (1 to 18) treatment cycles. The relationship of the dose intensity to tumor response and treatment duration is summarized in Table 1. Whereas the mean average drug dose remained relatively constant from cycle 1 to cycle 10, the dose intensity dropped progressively due to increasing treatment delay. The mean relative dose intensity was 0.70 for responders and 0.76 for non-responders. Treatment delay was important for patients who received either 2 cycles or more than 5 cycles. The reason for delay was prolonged acute toxicity for short treatment (massive diarrhea and dehydration in one patient, myelosuppression in 2 patients with diffuse bone metastases), or cumulative toxicity after the fifth cycle.

The treatment was well tolerated. All patients complained of the bad taste of liquid doxifluridine, but this did not limit the dose or duration of treatments. A nadir leucocyte count below 4000/mm$^3$ was observed in 16 patients, with 7 patients having a nadir count below 2000/mm$^3$ and 2 patients counts below 1000/mm$^3$. Leukopenia was always reversible, and was never accompanied by infectious complications. Seven of 8 patients who received 5 or more cycles had leukocyte nadir counts below 2000/mm$^3$, as compared with 2 of 9 of those with a shorter treatment. Ten patients had some degree of thrombocytopenia, but only one showed a nadir count below 50,000. WHO grades 3 or 4 diarrhea and emesis were observed in 2 patients and 1 patient, respectively. There were no toxic deaths.

Discussion

Treatment of advanced breast cancer with the oral combination of an alkylating agent, an anthracycline and a fluoropyrimidine as used in this trial may produce a tumor response similar to that generally observed following intravenous CAF, with a good and reproducible level of tolerance. Responses were observed in the primary tumor, in locoregional or distant skin lesions and in liver and bone metastases. The 4 patients with responding liver lesions experienced significant improvement in the quality of their lives during the remission. The toxic effects were those known to occur with the three agents when used alone. Leukopenia, the most frequently encountered, was always reversible. Diarrhea and emesis are typical side effects of doxifluridine and of idarubicin. Contrary to what might have been expected from the uneven bioavailability of oral treatments, the level of toxicity remained stable and predictable for all patients.

Table 1. Mean dose intensity relative to the protocol regimen.

<table>
<thead>
<tr>
<th>Relative mean dose intensity</th>
<th>Relative mean average drug dose</th>
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<tbody>
<tr>
<td>All patients</td>
<td>0.73</td>
</tr>
<tr>
<td>Responders</td>
<td>0.70</td>
</tr>
<tr>
<td>Non-responders</td>
<td>0.76</td>
</tr>
<tr>
<td>Patients with 2 cycles</td>
<td>0.63</td>
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<tr>
<td>Patients with 3 to 5 cycles</td>
<td>0.86</td>
</tr>
<tr>
<td>Patients with more than 5 cycles</td>
<td>0.58</td>
</tr>
<tr>
<td>Cycles 1 and 2</td>
<td>0.84</td>
</tr>
<tr>
<td>Cycles 3 and 4</td>
<td>0.77</td>
</tr>
<tr>
<td>Cycles 5 to 10</td>
<td>0.54</td>
</tr>
</tbody>
</table>

The significance of this study is limited, not only due to the small number of observations but also because of the selection of patients for whom oral treatment was particularly attractive. However, no prognostic factors associated with high rates of treatment response were detected in this selected subpopulation. To compare the treatment used here with the original CAF regimen would require a completely different approach.

With respect to quality of life, an oral treatment may be beneficial either for women with good performance status submitted to adjuvant treatment or, as in the present series, for those in advanced stages of disease. The subjective tolerance to the oral treatment used here was partially compromised by the bad taste of the drinkable doxifluridine solution, which might be replaced by capsules currently available in Japan. Poor patient compliance may limit the effectiveness of oral treatment. It is, however, generally observed that cancer patients are compliant, and this was confirmed in this trial by the drug related toxicity observed in all patients.

The results presented here need to be confirmed. An oral three-drug treatment of breast cancer might represent a useful alternative to currently available intravenous regimens. This, however, will depend on the availability of the agents used.

References


Modern adjuvant systemic therapy of breast cancer dates back to the early 1970s, and a few studies were activated even during the 1960s. Despite many years of trials (probably more than 200 randomized protocols have been activated as of today), consensus conferences and meta-analyses, this treatment approach still incites endless debate. Reports and reviews on adjuvant systemic therapy in breast cancer patients continue to appear almost daily in the scientific literature, often with contradictory interpretations. Wherein, then, lies the value of this latest addition to the series on 'Cancer Treatment and Research'?

With contributions from 26 authors, the volume is divided into four sections and two appendices. Appendix I reproduces the three consensus statements from the conferences held by the U.S. National Institute of Health/National Cancer Institute, and Appendix II lists the randomized clinical trials which are in the files of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in Oxford. The two appendices reflect the evolution of clinical trials with multimodality approaches for resectable breast cancer.

The rationale for adjuvant systemic therapy is the presence of micrometastatic disease well before clinical diagnosis of resectable cancer. The experimental and mathematical models on which its recognition is based, and explanations of further refinements of these models are discussed in the first chapter. Designing a study, analyzing its results and performing, meta-analyses requires appropriate statistical methods, as do the correct interpretation of reported findings. Readers will gain relevant information from the second chapter, ideally by reading it before the succeeding parts of this book.

Section II deals with the presentation of trial results. Most commonly, the effects of treatment are described in terms of relapse-free and total survival rates and absolute differences at the end of an observation period. Alternatively, and mainly when comparisons of different trials are attempted, proportional or ratio effects are best for describing treatment results. The relationship between proportional and absolute effects as well as the nature of the benefits are clearly explained in Chapter 3. The next three chapter summarize the various trials with endocrine manipulation and chemotherapy in both node-positive and node-negative tumors. Different points of view are expressed in these chapters, but, these diverse opinions represent a dissimilarity in the value assigned by each author to a 'modest' benefit in some patient subgroups rather than a real difference in the size of the benefit achieved.

Many of the reported findings are derived from the last meta-analysis performed in Oxford in 1990. However, since many of the treatment effects from individual trials are also summarized, readers will find it easier and more interesting to consider them in light of the 'averaged' results of the International Overview.

While the value of adjuvant systemic therapy in prolonging the lives of women with breast cancer is firmly supported by therapeutic results, other important aspects relative to this treatment modality have already emerged or begun to do so. Should adjuvant systemic therapy be reserved only for high-risk patients? What is the role of putatively new prognostic factors in selecting the appropriate treatment for given prognostic subgroups? Neoadjuvant chemotherapy is gaining acceptance also in women with resectable breast cancer; how to optimally integrate the different treatment modalities in patients for whom a conservative loco-regional approach is appropriate? If adjuvant chemotherapy and endocrine therapy are to become effective partners, how should they be delivered? All these topics are examined in Sections III and IV as well as models for weighing benefits and toxicities and considerations of the financial costs. If all the previously mentioned aspects represent the past and the present of adjuvant treatment modalities, the experimental bases for more futuristic therapies (e.g., manipulation of growth factors, modern immunotherapy, differentiation agents) are considered in the last three chapters.

Several books on breast disease have recently been published, both comprehensive and problem-oriented. I feel, however, that for both investigators and practicing oncologists interested in the adjuvant systemic therapy of breast cancer this is one of the most important and up-to-date reference books available.

Pinuccia Valagussa
Milan