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Advanced Breast Cancer—New Approaches to Treatment: Workshop Report

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INTRODUCTION

THIS review will briefly summarize the subjects addressed during the workshop and poster session on advanced disease and present the conclusions drawn on the basis of data from the literature and the data presented at the conference.

The following three major topics were discussed; (1) neoadjuvant approach for operable breast cancer, (2) locally advanced breast cancer and (3) metastatic disease.

NEOADJUVANT APPROACH

The rationale for the neoadjuvant approach as reviewed recently [1] includes interference with the potential of metastasis, provision of a tumor sensitivity test *in vivo*, a potential reduction in the development of drug resistant cells, a prevention of increase in tumor burden from the time of initial diagnosis to commencement of systemic therapy and possibly a limitation of the need for mastectomy.

Three studies of the neoadjuvant approach were presented at the meeting [2–4], one of which is a randomized study [4]. From the data available so far it can be concluded that the responsiveness of the primary tumor is comparable to that of metastatic disease. Mature data from randomized trials are still missing to enable conclusions about the efficacy of this approach compared to traditional postoperative systemic therapy.

LOCALLY ADVANCED DISEASE

Completed and on-going trials in locally advanced disease have been designed with the aim to define, in terms of local control and survival, the contribution of local therapy (radiotherapy, surgery) and systemic therapy. Two non-randomized [5, 6] and one randomized trial [7] were presented. The latter trial analyses, by a factorial two by two design, the contribution to radiotherapy of endocrine therapy, chemotherapy and combined chemo-endocrine therapy. It appeared from that study that the endocrine therapy (premenopausal: oophorectomy + prednisolone 7.5 mg daily for 5 years; postmenopausal: tamoxifen 20 mg daily for 5 years) improves survival, whereas no such survival advantage was observed with chemotherapy (CMF). All three treatments contributed to achievement of local control and survival, but the optimal sequence remains to be defined.

METASTATIC DISEASE

Endocrine therapy

New endocrine agents include the LHRH agonists and adrenal and aromatase inhibitors.

Blamey *et al.* [8] and Kaufman *et al.* [9] presented data to indicate that the response to the LHRH agonist, Zoladex, in premenopausal patients is close to 30%, similar to that achieved with oophorectomy [10] and tamoxifen [11]. Two randomized studies have demonstrated tamoxifen and oophorectomy to be equally effective [12, 13]. What needs to be analyzed in randomized trials is the efficacy of LHRH agonist compared to oophorectomy and compared to tamoxifen, and in this context also the combination of tamoxifen and LHRH agonist should be considered.

As far as trilostane is concerned, two presentations demonstrated that the drug seems to offer no advantage compared to other endocrine therapies [14, 15]. In addition, treatment with trilostane is associated with considerable toxicity. Therefore trilostane will not be a drug of interest compared to other adrenal or aromatase inhibitors.

It is now generally agreed that first line endocrine therapy in advanced breast cancer in postmenopausal patients should be tamoxifen, taking into

account efficacy, toxicity and response to second line endocrine therapy [16]. Recommended daily dose is 20–40 mg based upon the results of three randomized dose–response studies [17–19]. At this conference, it was further demonstrated [20] that an initial loading dose of tamoxifen (160 mg daily for 2 days) does not increase the efficacy of the 40 mg daily schedule.

Endocrine second line alternatives include gestagens and aminoglutethimide. A number of questions have been addressed in this context including the dose–response relationship, the contribution of hydrocortisone to the efficacy of the aminoglutethimide/hydrocortisone combination, and which drug to use. As far as the dose–response relationship is concerned, two presentations demonstrated medroxyprogesterone acetate (MPA), 300 mg vs. 900 mg [21] and 300 mg vs. 1000 mg [22] to be equally effective in terms of rate of response, time to progression and survival. Future trials should compare low dose gestagen with even higher doses in order to finally define the dose–response relationship. For aminoglutethimide (+ hydrocortisone) a randomized trial gave identical results with daily doses of 1000 and 500 mg [23]. The dose–response relationship and the contribution of hydrocortisone are also being analyzed in an on-going EORTC trial comparing 500 with 250 mg, both dose levels with and without hydrocortisone [24].

Three randomized studies compared aminoglutethimide to gestagens, medroxyprogesterone acetate (MPA) in two of the studies [25, 26], and megestrol acetate (MA) in the third study [27]. In two of the studies response rates were similar [25, 27], the third being too early to evaluate for response. Toxicities were observed with comparable frequency in two of the studies [26, 27], but in one study aminoglutethimide was significantly more toxic than MPA [25]. A remarkable result in the latter study was the observation that time to achievement of response was significantly shorter for MPA compared to aminoglutethimide.

Preliminary results from a multicenter study conducted in Sweden and Norway have indicated alternating treatment with tamoxifen and MPA to be superior to the sequential approach [28]. This question and also that of intermittent vs. continuous therapy are also addressed in an EORTC study just activated [29]. Patients known to have a receptor positive or unknown status start treatment with tamoxifen. At 4 months, patients with non-progressive disease are randomized to continuous or intermittent treatment with tamoxifen, or to intermittent, alternating treatment with MPA and tamoxifen.

Chemotherapy

The new cytotoxic agents can roughly be divided into two groups, the anthracyclines and others.

As far as the others are concerned, two posters were presented. Lonidamine, an indazole derivative, gave a response in three out of 18 patients with only moderate toxicity [30]. Ellipticinium was only marginally active (response in 4/31) with pronounced toxicities [31]. Also a recent study with TCNU was negative [32]. Patients who entered these studies were all heavily pre-treated, nevertheless it seems reasonable to do further research only for lonidamine.

The anthracycline derivatives include epirubicin, esorubicin, idarubicin, and THP-adriamycin. Also in this context, the anthracenedione derivative mitozantrone should be considered. Randomized trials of adriamycin vs. epirubicin [33, 34], including one presented at the conference [35], have now demonstrated the two drugs to be equally effective, but with hematologically equitoxic dose levels; other toxicities are less pronounced with epirubicin. Correspondingly, according to randomized comparisons of mitozantrone and adriamycin, the latter drug is marginally more active at the expense of more toxicity [36]. In a small phase II trial esorubicin was demonstrated not to be active [37]. For the other anthracycline derivatives the conference saw a number of phase II trials presented. Three trials analyzed the efficacy of idarubicin administered in different schedules, days 1–3 every 4 weeks [38], day 1 every 3 weeks [39], or weekly [40] with response rates of 35%, 13% and 31% respectively. In another phase II trial with THP-adriamycin, responses were observed in 28% of 32 patients [41]. Further studies should be undertaken with these derivatives and should also include comparisons with adriamycin in terms of efficacy and short and long-term toxicities.

Dose and schedule of anthracyclines are still areas of significant interest. Three papers were published in 1986 on weekly low dose adriamycin [42–44] reporting response rates from 31 to 52% with only minimal toxicity, and comparable results were reported at the conference with weekly low dose epirubicin [45].

So far no randomized studies to analyze the impact of dose and schedule of anthracyclines have been published, and one such study has recently been activated by the EORTC Breast Cancer Cooperative Group, which compares weekly low dose adriamycin (20 mg) with 3-weekly standard dose adriamycin (75 mg/m^2) [46].

A number of new combinations, the majority of which included THP/ADM [41], idarubicin [38, 47, 48] or mitozantrone [49–51] in combination with one or two older cytotoxic agents were presented. The majority of these trials are still

premature, however, so far none seems to be significantly superior to the established combinations.

The combination of cyclophosphamide, adriamycin and cisplatinum (CAP) was used in two studies. In a phase II study [52], including 37 patients, response was observed in 60%, and in a phase III study comparing CAP with CAF [53], response was observed in 67% and 41% of the patients, respectively. The difference in response rates is significant, however survival was comparable in the two groups. In discussing those trials, phase II data of cisplatinum in advanced previously untreated breast cancer were identified as being needed.

Dr. Engelsman presented the results of a recently completed EORTC study [54], comparing the classical CMF (oral cyclophosphamide days 1–14, 5-fluorouracil and methotrexate days 1 + 8, cycle repeated every 4 weeks) with i.v. CMF (all 3 drugs i.v. day 1 every 3 weeks). In this study, the classical CMF was superior to i.v. CMF in terms of response rate, time to progression and survival. However, retrospective analysis demonstrated the classical CMF to cause more pronounced hematological toxicity than i.v. CMF. The results of this important study should be confirmed in future studies.

The importance of treatment duration in non-progressive patients was analyzed in one study [55], which indicated that the patients did equally well when after 3 months treatment with mitozantrone was discontinued or continued. The same question is being addressed in an on-going EORTC study comparing 6 months vs. continuous CMF [56], and also in a Danish study comparing 6 months of CEF (cyclophosphamide, epirubicin, 5-fluorouracil) with 18 months of CEF [57].

The question of the dose–response relationship was addressed in only one study which compared different doses of epirubicin (E, 50 mg/m^2 vs. 75 mg/m^2) in the FEC combination [58]. Response rate was significantly higher with the high dose regimen, but survival figures were identical.

The timing of chemotherapy and endocrine therapy, especially with regard to recruitment by estrogenic stimulation, was previously been analyzed in two studies [59, 60], and two other studies were presented at the conference [61, 62]. This is an interesting approach, but it is still premature to conclude whether superiority can be achieved compared to standard combined chemo-endocrine therapy.

One possible approach to improve the results of chemotherapy in advanced disease is to alternate non-cross resistant combinations. Potential advantages are to delay cumulative toxicity of either combination and to delay emergence of resistant tumor cells. Dr. Paridaens [63] presented an on-going EORTC study designed to test the theoretical considerations of alternating chemotherapy presented by Goldie *et al.* [64]. In this study patients are randomized to alternating or sequential treatment with three different cytotoxic combinations. Conclusions must await further patient entry and prolonged time of follow up.

Diphosphonates

So far three different diphosphonates have been developed: hydroxyethylidenediphosphonate (HEDP = etidronate), disodiumdicholoromethylenediphosphonate (CL2MDP = clodronate) and aminohydroxypropylidenediphosphonate (APD).

In advanced breast cancer approx. 60% of the patients will suffer from lytic bone metastases caused by increase of osteoclastic bone resorption, probably in response to factors secreted by the tumor cells. The diphosphonates reduce the bone turn-over [65–67], and it is currently believed that they exert their effects by a combined effect on crystal behavior and osteoclastic function [68].

At this conference Van Holten-Verzandroort *et al.* [69] presented the data of a study in patients with bone metastases who were randomized to treatment with and without diphosphonate (APD, 150 mg twice daily). Within the time of observation significantly fewer episodes of hypercalcemia, fractures and deaths were observed in the APD treated groups.

Similar results were reported recently by Elomaa *et al.* [70, 71] who investigated the effect of long-term treatment with diphosphonates in advanced breast cancer. Seventeen patients received CL2MDP, 1600 mg per day for 12 months. These patients experienced fewer episodes of hypercalcemia, had fewer new bone metastases and bone fractures and required fewer analgesics compared to 17 control patients treated with placebo. Also after 1 and 2 years of observation fewer deaths were reported in the treated group (3 and 6, respectively) compared to the control group (8 and 13, respectively). The frequency of new non-osseous metastases was identical in the two groups.

Another poster demonstrated the effectiveness of diphosphonate (APD) in treating hypercalcemia [72]. Further studies should be undertaken with diphosphonate in advanced disease and should also be considered in primary disease in patients with high risk of developing bone metastases. These studies should also be designed with the aim to define the optimal duration and the long term effects of the therapy.

CONCLUSIONS

It appeared from the conference that no dramatic developments are immediately to be foreseen in the treatment of advanced breast cancer. However, with the treatments available today good palliation can be achieved, although many basic questions are still

to be addressed. To enable conclusions, carefully conducted large randomized trials are required. This in turn requires continued close co-operation between centers and countries, one example of which is represented by the EORTC Breast Cancer Co-operative Group.

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