Primary Endocrine Therapy for Locally Advanced Breast Cancer—Is it an Inferior Approach? Experience from Nottingham

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Abstract Treatment strategy for locally advanced primary breast cancer (LAPC) remains mainly multimodal involving neoadjuvant chemotherapy, surgery followed by radiotherapy and endocrine therapy, all given upfront. There have been few studies comparing this with a sequential treatment approach, for instance, using endocrine therapy as initial treatment. Based on small randomised clinical trials and local experience in Nottingham, primary endocrine therapy has been shown to produce very good early (response) and late (survival) outcome when used in ER positive, noninflammatory LAPC. This could be considered as a viable therapeutic option in appropriately selected patients.

Keywords Locally advanced primary breast cancer · Treatment · Endocrine therapy

Introduction

Locally advanced primary breast cancer (LAPC) was first described by Cushman Davis Haagensen in 1943 [1]. The

definition was based on the following one or more clinical features of skin ulceration, skin edema, skin nodules, inflammatory breast cancer, supraclavicular nodal metastases, arm edema, lump fixation to chest wall or the presence of axillary lymph nodes either measuring more than 2.5 cm in diameter or fixed in character. Hence LAPC consists of a heterogeneous group of breast disease.

However, the management approach does not target a specific type of LAPC but is applicable to generally any one type. The “conventional” therapeutic strategy is multimodal, comprising of neoadjuvant chemotherapy, surgery, postoperative radiotherapy and adjuvant hormone therapy, all given upfront. This approach has the disadvantages of morbidity associated with each modality of treatment and it is also unclear if all the patients will benefit from this combination of therapies as the tumour is heterogeneous in presentation.

Neoadjuvant chemotherapy renders a previous inoperable tumour operable and potentially allows the possibility of breast conservation. Evidence shows that this group however, may have an increased risk of local recurrence [2, 3].

The ideal regimen for neoadjuvant chemotherapy has been frequently evaluated and remains an ongoing quest. At the same time, there are few studies which evaluate alternative therapeutic approaches to LAPC. We aim to discuss the role of primary endocrine therapy as a possible option for initial treatment of LAPC, based on experience in Nottingham.

Endocrine therapy has a potential role as preoperative (neoadjuvant) therapy. More potent agents (third generation aromatase inhibitors and pure anti-oestrogen) may prove comparable or superior to chemotherapy in oestrogen receptor (ER) positive tumours.

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Setting the Scene—Multimodal Versus Sequential Treatment

The Nottingham breast unit conducted a cross-over trial comprising initial radiotherapy versus tamoxifen [4] (Fig. 1). This suggests that sequential use of single treatment modalities gave almost identical duration of control compared to both treatment modalities given together, as is the practice in upfront multimodal therapy (Figs. 2, 3). The risk of morbidities from multimodal treatment is thus reduced in this scheme of treatment. This study also showed that there was no difference in survival outcomes between the two groups (Fig. 4).

A subsequent randomised trial was carried out in Nottingham; comparing multimodal therapy versus primary endocrine treatment in LAPC [5]. Fifty-two patients were randomised to receive hormone therapy and 56 patients to receive multimodal treatment. Patients were unselected for ER status but data was available for ER positivity in 36 patients from the hormone treatment arm and 28 patients in the multimodality arm. For patients with inflammatory breast cancer, 6 received hormone treatment and 5 received multimodality treatment. The median follow-up was 45 months and 52 months in the hormone treatment group and multimodality group respectively.

The results of the trial showed that local “relapse” rate was higher in the hormone treatment group (measured as first local disease progression as the tumour was not “removed”) ($n=41$) when compared to the multimodality group (measured as true local recurrence) ($n=11$). However it should be highlighted that the rates of uncontrolled loco regional disease were similar in both groups ($n=3$, $n=2$, respectively).

There was no difference shown in either treatment groups in terms of number of metastases, time to metastases, number of breast cancer related deaths and overall survival.

The trial concluded that the hormone treatment group required further treatments to achieve a similar outcome to

Fig. 1 Nottingham Trial 1 (adapted from Ref [4])

Fig. 2 Nottingham Trial 1—Time to failure of first treatment (adapted from Ref [4])

the multimodality group. It was also evident that the major benefit for hormone treatment appeared to be in the ER positive patients.

Putting Primary Endocrine Therapy in Practice

The Nottingham practice for primary endocrine treatment in ER positive tumours were based on the trial mentioned earlier [5] and its application on patients who had ER positive tumours [6]. Inflammatory breast cancer unselected for ER status and all ER negative patients were treated with neoadjuvant chemotherapy if medically fit. Inoperable ER positive tumours were offered primary endocrine treatment and similarly for ER positive operable tumours unfit for surgery/chemotherapy. Patients who were ER positive and fit for surgery were offered the option of primary endocrine treatment, or chemotherapy as part of multimodal treatment.

Between 1988–2007, a total of 195 patients with ER positive, non-inflammatory LAPCs received primary endocrine therapy as the treatment of choice, due to inoperability, patient choice or inclusion in the above-mentioned trial. The initial endocrine agent was tamoxifen or goserelin plus tamoxifen for post and pre-menopausal patient's respectively. Tamoxifen was replaced by anastrozole since 2003. Clinical response was assessed on follow-up accord-

Fig. 3 Nottingham Trial 1—Time to failure of second treatment (adapted from Ref [4])

Fig. 4 Nottingham Trial 1—Survival outcome (adapted from Ref [4])

ing to International Union of Cancer (UICC) [7] criteria in a dedicated LAPC clinic.

The median clinical size of the tumour was 6 cm (2–9). All patients had ER positive tumours, with a median H-score of 190 (30–300). At median follow-up of 61 months (3–227), 185(95%) of patients derived clinical benefit (complete response, partial response or stable disease) for a minimum duration of 6 months, from primary endocrine therapy and 10 patients progressed early. Eight patients had complete response and 39 patients had partial response and the majority of the patients had stable disease (138). Of these 185(95%) patients, 41(21%) eventually received other modalities of treatment.

Five-year overall survival was 76%. (Fig. 5) and 5-year breast cancer specific survival was 86%. (Fig. 6). Comparison of this study was made with another study from this institute on anthracycline based neoadjuvant chemotherapy as part of multimodal treatment in LAPC, with the understanding that these two groups of patients had different tumours due to treatment selection [8]. Despite

Fig. 5 Kaplan-Meier survival curve for overall survival of patients on primary endocrine therapy (adapted from Ref [6])

Fig. 6 Primary endocrine therapy-breast cancer specific survival (adapted from Ref [6])

this it is worth noting that there was no significant difference between the two groups with regard to 5-year breast cancer specific survival (primary endocrine therapy 86% vs. neoadjuvant chemotherapy 85%; $p=0.989$) (Fig. 7).

This study hence supports that in ER positive LAPC, primary endocrine therapy is an alternative therapeutic option for selected patients.

Conclusion

Primary endocrine therapy can produce very good early (response) and late (survival) outcome when used in ER positive, non-inflammatory LAPC. This can be considered as a viable therapeutic option in appropriately selected patients. Future studies in this field will help validate the benefit of this approach as opposed to the conventional multimodal treatment in LAPC.

Fig. 7 Breast cancer specific survival-primary endocrine vs multimodal treatment (Anthracycline)

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