Chapter 2

Ovarian ablation

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Key points

- Ovarian ablation can be achieved through oopherectomy, irradiation, or via medical ablation (chemotherapy-induced or with the administration of luteinizing hormone releasing hormone (LHRH) agonists).
- An oopherectomy is effective in reducing levels of oestrogen to a menopausal state, but this procedure is irreversible.
- Radiation therapy to the ovaries can induce postmenopausal oestrogen levels; however this technique is slow to take effect and is not 100% effective.
- LHRH agonist therapy can induce reversible ovarian suppression and is well tolerated.
- Studies have reported that ovarian ablation/suppression reduces the recurrence and mortality rates in the treatment of early breast cancer.

2.1 Overview

Ovarian ablation has been utilized for over 100 years in the treatment of breast cancer. In 1896, Dr. Beatson demonstrated a treatment response after performing an oopherectomy in a premenopausal woman with advanced breast cancer (Sainsbury, 2003). Since then, numerous randomized trials have been conducted to evaluate the role of ovarian ablation in the treatment of early and advanced disease. While many of these trials involved smaller numbers of patients, the Early Breast Cancer Trialists Collaborative Group (EBCTG) recently published updated reports on more than 8000 women treated with either ovarian ablation via oopherectomy, irradiation, or LHRH agonists (EBCTG, 2005). These results will be presented later. In this chapter, we will discuss the clinical data using all of these modalities for ovarian ablation in premenopausal women with early or advanced breast cancer.

2.2 Surgical oopherectomy

As described previously, an oopherectomy was first performed in 1896 on a patient with advanced breast cancer (Sainsbury, 2003). However, it was not until approximately 60 years later that oestrogen (or the lack of it) was found to be responsible for this treatment effect (Jordan, 1999). Surgical ablation does offer immediate and effective results in reducing the levels of oestrogen to a menopausal state and the outcome is permanent. One disadvantage is with the surgery itself. This requires general anesthesia and is not without risk. In initial studies, perioperative mortality rates were as high as 5%. With modern surgical techniques, this risk is much less (Prowell and Davidson, 2004). Some would also consider the irreversibility imposed with an oopherectomy a disadvantage, especially in women who have a desire to preserve ovarian function for fertility. Osteoporosis can also be a long-term toxicity due to the postmenopausal levels of oestrogen. Oopherectomy as a treatment in premenopausal breast cancer is a viable option. The National Comprehensive Cancer Network (NCCN) recommendations include oopherectomy as a treatment option in premenopausal patients plus/minus tamoxifen for 2–3 years. In the metastatic setting, ER/PR-positive premenopausal patients can also be considered for ovarian ablation if they have not received prior anti-oestrogens or if it has been greater than one year since anti-oestrogen therapy (NCCN v.2.2006).

2.3 Radiation therapy

Ovarian irradiation as a modality for ablation has been utilized to achieve postmenopausal levels of oestrogen for over 70 years. In general, radiation can be easily administered; however, the degree of ovarian ablation is dose and age dependent. This technique can produce slow responses in reducing oestrogen levels and may produce incomplete or reversible ablation. Failure rates as high as 35% have been reported in women <35 years of age (Leung *et al*., 1991). In another study, 13% of women regained ovarian function after irradiation. Common side effects can include: diarrhoea, abdominal cramping, and urinary frequency. There is limited enthusiasm for this treatment modality in the United States; however, this form of ablation is offered as an option in Canada and Western Europe (Prowell and Davidson, 2004). Recommendations by the NCCN are the same as listed above in 2.2. (NCCN, v.2.2006)

Unfortunately, the benefit of oopherectomy, ovarian irradiation, or medical ovarian suppression has not been studied in large clinical trials. It is generally believed that the different modalities of ovarian ablation (oopherectomy or irradiation) are considered equivalent in

treatment effect based on indirect comparisons. The largest group studied to date is included in a meta-analysis conducted by the EBCTG (EBCTG, 2005). Results have recently been published comprising 15-year survival data regarding the effects of chemotherapy and hormonal therapy in the treatment of early breast cancer. These data involve studies initiated prior to 1995 and are the final results of the 2000 EBCTCG meta-analysis. In this overview, many different treatment settings were evaluated, one being the use of ovarian ablation/suppression for the treatment of early breast cancer. Almost 8000 women <50 years of age have participated in trials consisting of ovarian ablation either by surgery, radiation, or medical management. These studies have included both ER-positive and negative patients. When these data are combined, both the effects of recurrence and breast cancer mortality are decreased significantly with the use of ovarian ablation or suppression ($2p < 0.00001$ and $2p = 0.004$, respectively). Compared to the previous updates by the EBCTG, these results are not as robust (EBCTG, 1996). This could be due to ovarian ablation generally not being tested against effective systemic therapy. Most of these trials included chemotherapy consisting of CMF (cyclophosphamide, methotrexate, fluorouracil) like regimens and not anthracycline containing therapies, which are considered to be superior in this setting. In the updated analysis, there was no indication of a superior method of achieving postmenopausal levels of oestrogen with either ablation or suppression; however, the effects appear to be smaller in the studies where both treatment arms received chemotherapy versus those patients who did not receive chemotherapy. One reason for this may be the benefit that women incur with chemotherapy-induced amenorrhoea. Updates will continually be evaluated every 5 years by the EBCTG.

2.4 Medical ovarian suppression

With the advent of LHRH agonists, a change in the method of achieving ovarian ablation has evolved. Goserelin (Zoladex®), leuprolide (Lupron®), triptorelin (Trelstar®), and buserelin offer an option with medical ovarian suppression. These agents have the advantage of producing reliable and reversible suppression of ovarian function, which may help limit undesirable long-term side effects such as osteoporosis in patients and may help maintain fertility in patients wanting to conceive after receiving chemotherapy. The pharmacologic action of LHRH agonists occurs at the level of the hypothalamic pituitary axis. Under normal circumstances, the hypothalamus releases LHRH, which in turn regulates the pituitary to release gonadotropins. These gonadotropins ultimately stimulate ovarian function. With the chronic administration of an LHRH agonist, there

Table 2.1 Advantages and disadvantages of different modalities of ovarian ablation

Modality	Advantages	Disadvantages	Dose
Oopherectomy	1. Immediate 2. Effective	1. General anesthesia 2. Irreversible	– –
Irradiation	1. Easily administered	1. Can be incomplete 2. Slow response	– –
Medical ablation:			
Goserelin	1. Easily administered 2. Reversible		3.6mg SC monthly
Leuprorelin	1. Easily administered 2. Reversible		11.25mg IM every 3 months
Buserelin	1. Easily administered 2. Reversible		6.6mg SC every 2 months

SC = subcutaneous, IM = intramuscularly

is an initial surge in gonadotropins and oestrogen levels. The body counteracts this surge via a negative feedback loop leading to an overall decline of circulating oestrogens to a postmenopausal state (Sainsbury 2003). Goserelin is the only agent approved in the United States for the treatment of advanced breast cancer. Common side effects of the LHRH agonists include: injection site reaction, menopausal symptoms, hot flashes, and myalgias (Dees and Davidson 2001). A summary of advantages and disadvantages of the different ovarian ablation techniques is presented in Table 2.1. LHRH agonists have been studied as an alternative to chemotherapy, either administered alone, in combination with tamoxifen, or to maintain ovarian suppression in women who resumed menses after completion of chemotherapy.

2.5 Chemotherapy induced ovarian ablation

Another form of medical ovarian ablation includes those individuals who experience temporary or permanent ovarian dysfunction after receiving chemotherapy. Chemotherapy related amenorrhoea (CRA) is a well-known toxicity with alkylating agents. Approximately 68% of patients given CMF chemotherapy will undergo CRA. Rates of permanent amenorrhoea have been reported to range from as low as 40% in women <40 years of age to >90% in those >40 years (Prowell and Davidson 2004). Retrospective analysis have even suggested

that patients undergoing CRA have a lower recurrence rate and improved survival but this has not been confirmed in well-designed studies. This is currently being evaluated in ongoing trials. To date, numerous studies have been conducted comparing the different modalities of ovarian ablation either used as a single modality or combined with chemo and/or endocrine therapy for the treatment of ER-positive breast cancer in premenopausal women. For a thorough review of the data, refer to an overview of ovarian ablation in the treatment of adjuvant, early breast cancer (Jones and Buzdar, 2004).

2.6 Ovarian ablation as an alternative to chemotherapy

Early adjuvant trials have studied the benefit of ovarian ablation compared to chemotherapy. One of the first trials to attempt this was in a study conducted by the Scottish Cancer Trials Breast Group (Scottish Cancer Trials Breast Group, 1993; Thomson *et al*., 2002). Premenopausal patients were randomized to receive either adjuvant ovarian ablation (oopherectomy or irradiation) or CMF chemotherapy (cyclophosphamide 750mg/m^2, methotrexate 50mg/m^2, and fluorouracil 600mg/m^2) intravenously once every 3 weeks for 6 cycles. Patients were included regardless of ER/PR status. With a median follow-up of 13.9 years, there was no difference in OS between the two treatment arms (HR [hazard ratio] = 1.01; 95% CI = 0.74–1.37). In a further analysis, results identified that ER-negative patients did not incur any benefit from treatment with an oopherectomy and were actually at an increased risk of death when treated with surgery alone (HR 2.33; 95% CI = 0.30–4.20). The Zoladex Early Breast Cancer Research Association trial (ZEBRA, which is one of the largest trials adjuvant trials to date) compared the efficacy of an LHRH agonist (goserelin x 2 years) versus chemotherapy (CMF) in the treatment of adjuvant breast cancer (Kaufmann *et al*., 2003). With a median follow-up of 7.3 years, updated efficacy analyses have been conducted and the findings were similar to previous 6-year results. In the overall population, DFS was significantly better with CMF compared to goserelin ($p = 0.007$). Both treatment regimens were similar in ER-positive patients ($p = 0.597$), and in ER-negative patients goserelin would found to be inferior to CMF ($p = 0.0001$). Across the population, there was no difference in OS with goserelin or CMF ($p = 0.137$). ER-negative patients continually illustrated significantly better OS with CMF versus goserelin ($p = 0.009$). These data continue to confirm the lack of efficacy of hormonal therapy in ER-negative breast cancer.

Another smaller trial, the Takeda Adjuvant Breast Cancer Study with Leuprorelin Acetate (TABLE) study was designed to also

compare ovarian suppression with an LHRH agonist versus CMF chemotherapy (Schmid *et al*., 2002). At 2 years, the data is available on only 227 of the 589 randomized patients. With the short follow-up, no difference was demonstrated with recurrence-free survival or OS. More mature data will be needed to critically evaluate these study results. With these data, ovarian suppression is considered an effective alternative to CMF chemotherapy for the treatment of premenopausal, node-positive, ER-positive, early breast cancer.

2.7 LHRH agonists in combination with tamoxifen versus chemotherapy

Utilizing combination endocrine therapy consisting of an LHRH agonist and tamoxifen compared to chemotherapy has also been evaluated. The Austrian Breast Cancer Study Group (ASCSG) 05 conducted a trial in women who were randomized to receive classic CMF chemotherapy x 6 cycles or goserelin plus tamoxifen for 5 years regardless of ER/PR or lymph node status. At a median follow-up of 5 years, OS between the two treatment arms were not significantly different ($p = 0.19$). Recurrence-free survival was significantly better in those patients receiving goserelin plus tamoxifen compared to CMF ($p = 0.037$). When evaluating ER-positive patients only, recurrence-free survival was significantly better with the hormonal arm compared to chemotherapy ($p = 0.037$) and no difference was seen in OS between treatment arms ($p = 0.195$).

The Italian Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group Trial (GROCTA 02 Trial) also conducted a study in a similar fashion. With a median follow-up of 6.3 years, 37% of patients had relapsed and 18% of participants had died. No difference in DFS or OS was identified between treatment arms ($p = 0.8$, $p = 0.3$ respectively).

The question regarding utilization of an anthracycline-containing regimen compared to ovarian ablation has not been fully studied. A trial conducted by the French Adjuvant Study Group (FASG 06), evaluated the role of complete hormonal blockade (triptorelin 3.75mg IM every 28 days plus tamoxifen 30mg daily for 3 years) versus anthracycline-based chemotherapy (FEC50 (fluorouracil 500mg/m^2, epirubicin 50mg/m^2, and cyclophosphamide 500mg/m^2 IV every 21 days x 6 cycles without hormonal therapy) in early breast cancer patients (Roche *et al*., 2006). Patients with 1–3 positive lymph nodes and positive ER and/or PR status were enrolled. Five hundred and fifty-three patients were needed for the study to be appropriately powered. Over the course of 8 years, only 333 patients were enrolled. Due to slow accrual, the trial was closed. With a median follow-up of 83 months, DFS between both groups were similar (76% with

hormonal therapy versus 72% with chemotherapy; p = 0.13) and OS was not found to be statistically significantly better (88% versus 81%; p = 0.20, respectively). Due to the small numbers of patients enrolled, the trial was not adequately powered to demonstrate statistical significance between treatment arms. With these limited data, it is hard to conclude if women treated with ovarian ablation plus tamoxifen versus those given an anthracycline containing-regimen have better outcomes.

2.8 Ovarian suppression after chemotherapy

Numerous trials have been conducted evaluating the benefit of the adjuvant use of ovarian suppression in women whose ovarian function continued after completing chemotherapy. The Zoladex in Premenopausal Patients (ZIPP) trial combined data from four international collaborative groups (n = 2648) (Cancer Research Campaign Breast Cancer Trials Group, Stockholm Breast Cancer Study Group, South East Sweden Breast Cancer Group, and Gruppo Interdisciplinaire Valutazione Interventi in Oncologia). After patients received their initial therapy (surgery/radiation/chemotherapy), they were randomized to four treatment arms consisting of 1) goserelin (G) for 2 years; 2) tamoxifen (T) for 2 years; 3) G for 2 years plus T for 2 years; or 4) no further therapy (Baum *et al.*, 2006). With a median follow-up of 5.5 years, the event-free survival was statistically significant better with goserelin versus those patients who did not receive goserelin (HR = 0.80; 95% CI = 0.69–0.92; p = 0.002). Overall survival was also statistically improved with goserelin compared to no LHRH agonist (HR = 0.81; 95% CI = 0.67–0.99; p = 0.038). This study demonstrated that the addition of goserelin to standard treatment is more effective than standard therapy alone in the treatment of premenopausal, early breast cancer patients.

The Intergroup Trial (INT-0101) also investigated the effects of adjuvant chemo/hormonal therapy in early breast cancer patients with positive lymph nodes and ER and/or PR-positive disease (Davidson *et al.*, 2005). Patients were randomized to receive chemotherapy consisting of: CAF – cyclophosphamide 100mg/m^2 orally x 14 days, doxorubicin 30mg/m^2 IV on days 1 and 8, and fluorouracil 500mg/m^2 IV on days 1 and 8 every 28 days x 6 cycles, or CAF + G x 5 years, or CAF + G + T x 5 years. With a median follow-up of 9.6 years, CAF + G + T significantly reduced recurrence rates (HR = 0.73 95% CI = 0.59–0.90; p <0.01). With only G added to CAF chemotherapy there was not a significant decrease in recurrence (HR = 0.93, 95% CI = 0.76–1.14; p = 0.25). Overall survival in both comparison groups: CAF + G versus CAF alone and CAF + G + T versus CAF + G was not statistically significant (p = 0.14 and p = 0.21 respectively).

In retrospective subgroup analyses, a benefit was identified with the addition of G + CAF in women <40 years of age. Those patients >40 years of age showed little benefit. These subgroup analyses were small and underpowered to make conclusive statements. One noted limitation to the study was the lack of a chemotherapy plus tamoxifen alone arm. This would be considered standard of care; however, when the trial was initiated, routine use of tamoxifen in premenopausal patients was not customary. Also noted by the authors was a lack of an anthracycline containing chemotherapy arm, which is now considered standard of care making it difficult to compare results to adjuvant chemo/hormonal therapy regimens today.

The International Breast Cancer Study Group Trial (IBCSG VIII) compared three different treatment arms in 1063 premenopausal, node-negative, ER-positive and/or negative women with early breast cancer (Castiglione-Gertsch *et al*., 2003). After completing local therapy, patients were randomized to classic CMF x 6, G x 2 years, or CMF followed by G for 18 months. With a median follow-up of 7 years, no difference in DFS was observed among the three treatment arms. CMF alone resulted in a DFS of 82% (95% CI = 78–86%). The CMF arm followed by G for 18 months incurred a DFS of 87% (95% CI = 83–91%) versus 85% in those patients who only received G for 24 months (95% CI = 75–84%). Further analysis of patients with ER-positive disease, demonstrated equivalent 5-year DFS rates in those receiving CMF or G alone (81%, 95% CI = 76–87%; 81%, 95% CI = 76–87%, respectively). DFS with sequential G after CMF was 86% (95% CI = 82–91%). Cumulative data across all arms revealed a statistically significant improvement in DFS compared to no treatment (77% versus 60%; p = 0.02). Like the previously mentioned study, one limitation to this trial was the lack of a treatment arm containing tamoxifen, as this was initiated prior to the routine use of tamoxifen in premenopausal patients.

Currently, three other trials are being conducted by the IBCSG to help better answer some of these ongoing questions. These studies were initiated in March 2003 to evaluate chemotherapy, ovarian suppression, and other endocrine therapies (tamoxifen or aromatase inhibitors) in the adjuvant treatment of early breast cancer. The Suppression of Ovarian Function Trial (SOFT) was designed for women who maintain ovarian function after surgery or after completing chemotherapy (Francis *et al*., 2003). Women are randomized to three treatment arms: tamoxifen 20mg daily for 5 years; tamoxifen + ovarian suppression with either surgical oopherectomy or triptorelin 3.75mg every 28 days for 5 years; or lastly exemestane 25mg daily for 5 years. The second of these trials, is the Tamoxifen and Exemestane Trial (TEXT trial). This study is for those women who plan to receive their adjuvant therapy concurrently with ovarian suppression

(triptorelin) from the start. After their chemotherapy, they are then randomized to receive either tamoxifen or exemestane. The last of the three trials is the Premenopausal Endocrine Responsive Chemotherapy (PERCHE) study. This trial includes two treatment arms: ovarian suppression plus hormonal therapy (tamoxifen or exemestane) or a triplet arm consisting of chemotherapy, ovarian suppression, and hormonal therapy (tamoxifen or exemestane). These trials are currently underway and target accruals include 3000 patients for the SOFT trial, 1875 for the TEXT trial, and 1750 for the PERCHE trial (Francis *et al*., 2003).

Unlike the previously mentioned trials, the Mam-1 GOCSI study was unique in that it incorporated an anthracycline into the chemotherapy regimen. Premenopausal women with node positive, early breast cancer were randomized to 4 arms: CMF (group A); doxorubicin followed by CMF (group B); CMF followed by goserelin + tamoxifen (group C); and doxorubicin followed by CMF followed by goserelin + tamoxifen (group D) (De Placido *et al*., 2005). With a median follow-up of 6 years, the addition of goserelin and tamoxifen after chemotherapy produced statistically significant improvements in DFS (HR = 0.74; 95% CI = 0.555–0.987; p = 0.044). Overall survival was not significant (HR = 0.84; 95% CI = 0.54–1.32; p = 0.48). Due to slow accrual, the study was closed and with a small sample size, the study was not adequately powered.

A lack of benefit was demonstrated by a group from the Institut Gustave-Roussy evaluating the addition of ovarian suppression to adjuvant chemotherapy (Arriagada *et al*., 2005). Chemotherapy regimens were given at the discretion of the study centres but generally included an anthracycline containing regimen or CMF-like regimen. Ovarian suppression was accomplished by oopherectomy, irradiation, or medically with triptorelin. At a median follow-up of 10 years, DFS in both groups was 49% (95% CI = 44–54%; p = 0.51). Overall survival was similar with 66% in the ovarian suppression arm compared to 68% in the control arm (p = 0.19).

In summary, all of the trials discussed above demonstrate ovarian ablation/suppression as an effective means of reducing the risk of recurrence in ER-positive early breast cancer. A summary of these results can be found in Table 2.2. These studies support the use of ovarian suppression as an alternative to CMF like chemotherapy in this subset of patients. Unfortunately, many of these trials discussed included ER-negative patients and in many of them tamoxifen was not included as a treatment arm as that was not the standard of care at the time the studies were initiated. Today in the adjuvant setting, tamoxifen is routinely utilized in premenopausal ER-positive patients. In addition, many of the trials did not compare endocrine therapy to

Table 2.2 Summary of disease-free survival with ovarian suppression in early breast cancer trials

Study (number of patients)	Treatment arms	HR (95% CI) p value	Results
ZEBRA* (n = 1640)	G x 2 yrs CMF	1.05 (0.88–1.24) p = 0.597	In ER (+) pts, G = CMF.
TABLE (n = 589) (Schmid *et al*., 2002)	L x 2 yrs CMF	2 yr DFS 59.1% vs. 45.3%	No difference in recurrent free survival
ABCSG* (n = 1034)	G + T × 5 yrs CMF	1.40 (1.06–1.87) p = 0.017	G + T significantly better than CMF at 5 yrs in ER (+) pts
GROCTA* (n = 224)	G x 2 yrs + T × 5yrs CMF	0.94 (0.60–1.47) p = 0.80	G + T similar to CMF
FASG 06 (n = 333) (Roche *et al*., 2006)	Triptorelin + T × 3 yrs FEC	Recurrence 76% vs. 72% p = 0.13	Trial closed early
ZIPP (n = 2710) (Baum *et al*., 2006)	G x 2 yrs T x 2 yrs G x 2 yrs + T × 2 yrs	0.80 (0.69–0.92) p = 0.002	Addition of G to standard therapy is more effective than standard therapy alone
INT-0101 (n = 1503) (Davidson *et al*., 2005)	CAF alone (a) CAF → G × 5 yrs (b) CAF → G + T × 5 yrs (c)	(b vs. a) = 0.93 (0.76–1.12) p = 0.22 (c vs. b) = 0.74 (0.60–0.91) p <0.01	Triplet therapy improved DFS but not OS
IBCSG VIII (n = 1063) (Castiglione-Gertsch *et al*., 2003)	CMF (a) G × 24 months (b) CMF → G × 18 months (c)	(a vs. b) = 1.13 (0.83–1.53) p = 0.44 (c vs. b) = 0.71 (0.52–0.99) p = 0.04	CMF → G was better than treatment alone
Mam-1 GOCSI (n = 466) (De Placido *et al*., 2005)	CMF alone A → CMF CMF → G + T × 2yrs A → CMF → G + T × 2 yrs	G + T after chemo 0.74 (0.555–0.987) p = 0.040	Combination G + T after chemo was significantly better than chemo alone
Arriagada, *et al*., (n = 926) (Arriagada *et al*., 2005)	Chemo → OSupp/OA Chemo alone	HR (NR) Recurrence = 49% P = 0.51	Ovarian suppression after chemo was not beneficial

* = Studies reviewed in Jones and Buzdar (2004). A = adriamycin; ABCSG = Austrian Breast and Colorectal Cancer Study Group; CAF = cyclophosphamide, adriamycin, fluorouracil; CMF = cyclophosphamide, methotrexate, fluorouracil; DFS = disease free survival; FASG 06 = French Adjuvant Study Group; FEC = fluorouracil, epirubicin, cyclophosphamide; f/u = follow up; G = goserelin; GOCSI = Gruppo Oncologico Central Sud Isole; GROCTA = Gruppo di Recerca in Oncologia Clinica e Terapie Associate; HR = hazard ratio; IBCSG = International Breast Cancer Study Group; INT = Intergroup Trial; L = leuprorelin; NR = not reported; OA = ovarian ablation; OS = overall survival; OSupp = ovarian suppression; T = tamoxifen; TABLE = Takeda Adjuvant Breast Cancer Study; ZEBRA = Zoladex Early Breast Cancer Research Association; ZIPP = Zoladex in Premenopausal Patients

anthracycline-containing regimens or combine endocrine therapy with anthracycline chemotherapy. Data from the SOFT, TEXT, and PERCHE trials will help us fully answer questions not addressed in the previous studies, such as the optimal duration of ovarian suppression with LHRH agonists, what is the benefit of combined hormonal therapy after chemotherapy, and in those women who regain ovarian function after chemotherapy, what is the value of ovarian ablation?

2.9 Ovarian ablation in the metastatic setting

Ovarian ablation has been a long-established modality of treatment for premenopausal, advanced breast cancer patients. As in the adjuvant setting, many different combinations have been studied including tamoxifen alone or in combination with ovarian ablation/suppression, or with ovarian suppression alone versus oopherectomy. These data have been collected for many years and so meta-analyses have been performed. Blamey *et al.* reviewed 29 clinical trials evaluating women who had received goserelin as a first line treatment option for advanced breast cancer (Blamey *et al.*, 1992). Three hundred and thirty three women were identified. Objective clinical response (complete + partial response) was identified in 36.4% of patients with a median duration of response of 44 weeks. Median overall survival was 33.1 months in ER-positive patients (range 0.8–69) and 15.9 months in ER-negative patients (range 1–44.4). These responses were considered comparable to historical outcomes with oopherectomy or irradiation in a similar population. With these data, ovarian suppression demonstrated a role for first-line therapy in this group of patients.

Tamoxifen compared to ovarian ablation (either surgery or radiation induced) alone as first-line treatment of premenopausal, metastatic breast cancer has also been evaluated. A meta-analysis conducted by Crump *et al.* identified 4 clinical trials answering this question. (Crump *et al.*, 1997) Two hundred and twenty ER-positive or negative women were included in this analysis. No difference in overall response rate between treatment arms was observed ($p = 0.94$). Patients were allowed to cross over to the other treatment arm, so conclusions regarding overall survival advantages could not be evaluated. The conclusion by the authors stated that the efficacy of tamoxifen is similar to ovarian ablation when used as first-line therapy in premenopausal women with metastatic breast cancer.

The last group of data comes from trials studying the benefit of combined endocrine therapy with tamoxifen plus ovarian suppression compared to ovarian suppression alone. Klijn and colleagues

Table 2.3 Summary of ovarian ablation in premenopausal, metastatic breast cancer patients

Studies	Patients	Results
Goserelin alone (Blamey *et al*., 1992)	333	CR + PR = 36.4% Median duration of response = 44 weeks Median OS = 33.1 months in ER (+) and 15.9 months in ER (–) patients
T compared to OA (Crump *et al*., 1997)	220	No difference in overall response rate Patients were allowed to cross over between treatment arms
T + OA compared to OA alone (Klijn *et al*., 2001)	506	Combination endocrine therapy demonstrated significant objective responses (39% vs. 30%, p = 0.03) Survival was better with combined therapy (p = 0.02; HR = 0.78, 95% CI 0.63–0.96)

CR = complete response; ER = oestrogen receptor; OA = ovarian ablation; OS = overall survival; PR = partial response; T = tamoxifen

have evaluated 4 randomized studies in a meta-analysis comprised of 506 women with advanced breast cancer (Klijn *et al*., 2001). With a median follow-up of 6.8 years at the time of publication, the combination arm exhibited significant differences in objective responses (39% versus 30%; p = 0.03) and in survival (p = 0.02; HR = 0.78; 95% CI = 0.63–0.96) compared to ovarian suppression alone. These results demonstrate that ovarian suppression with an LHRH agonist combined with tamoxifen is the preferred hormonal manipulation in a premenopausal, metastatic breast cancer patient. For a summary of all of these results, see Table 2.3.

2.10 Conclusions

Ovarian ablation has been utilized in the treatment of breast cancer for over 100 years. This modality of therapy can be accomplished via oopherectomy, irradiation, or medical management. Surgery and radiation are effective treatments; however, they do have disadvantages. Oopherectomy is permanent and can cause long-term side effects and radiation is dose/age specific and may not be fully effective. Unlike these modalities, LHRH agonists are reversible and generally produce few side effects. LHRH agonists have demonstrated to be as effective as CMF chemotherapy in the adjuvant treatment of premenopausal early breast cancer. With the addition of tamoxifen to ovarian ablation efficacy has also improved compared to

CMF-containing regimens. Numerous trials have been conducted evaluating ovarian suppression after chemotherapy. Many did not contain tamoxifen as a standard treatment arm due to the studies beginning prior to the standard use of tamoxifen in premenopausal patients. The SOFT, TEXT, and PERCHE trials are currently underway to evaluate different LHRH agonists and other hormonal therapy combinations with or without chemotherapy to help answer these lingering questions. In the metastatic setting, combination therapy with tamoxifen and a LHRH agonist can be considered the preferred first-line treatment option in premenopausal women. Many different options are available for ovarian ablation in these treatment settings and current studies may help us better guide therapy once results are released.

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