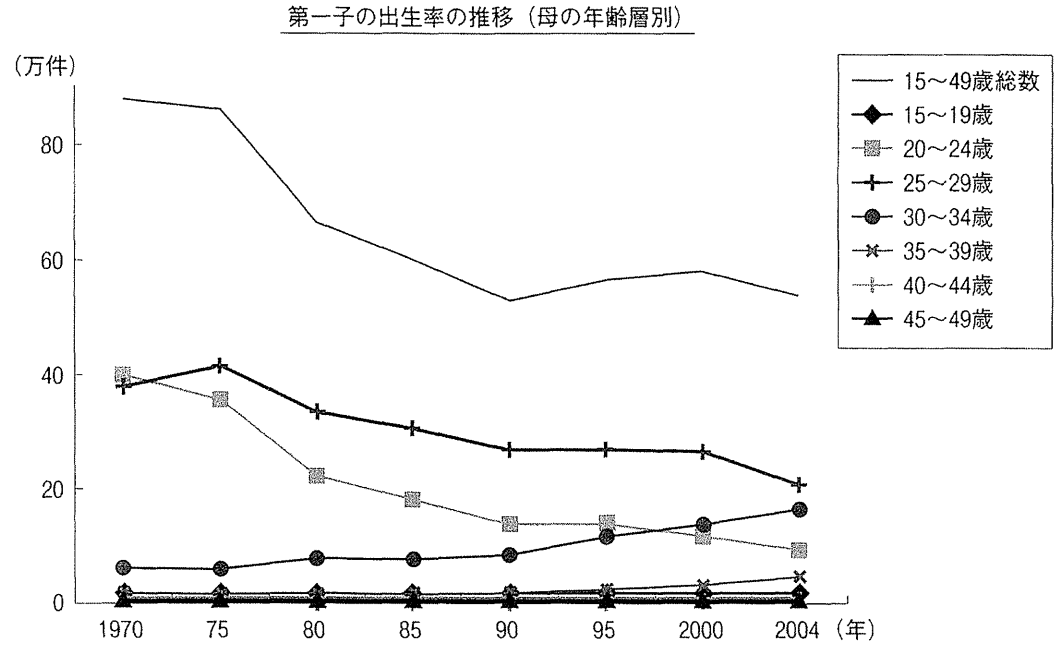


（備考）1．厚生労働省「人口動態統計」により作成．ただし，2004年は概数．
2．母の年齢層別の出生数のうち，出生順位（同じ母親がこれまでに生んだ出生子の総数について数えた順序）が第一子となる子の出生数．

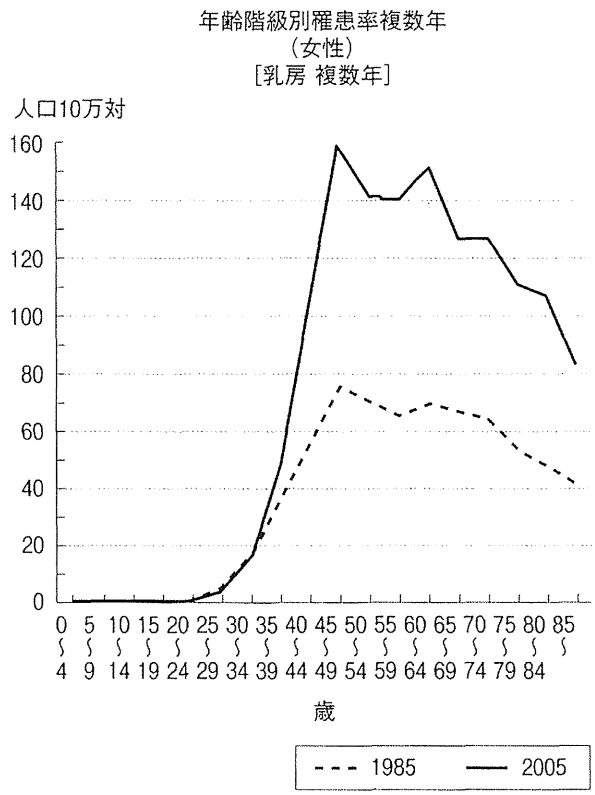
図1　初産年齢の推移
（国民生活白書「子育て世代の意識と生活」http://www5.cao.go.jp/seikatsu/whitepaper/h17/01_honpen/index.html より引用（Accessed 2013-01-18））

1．妊娠期の乳癌

妊娠期乳癌はまれであり，1万の出生に対し1.3人と報告されている[8]．妊娠期の乳房は進行癌で発見されることが多く，またホルモンレセプター陰性・HER2陽性乳癌が多いと報告され予後が悪いと考えられていたが，臨床病理学的因子を調整すると非妊娠期乳癌と予後に差はないという報告も多い[9~13]．遠隔転移のない妊娠期乳癌についてはNCCNガイドラインに収載されているが，局所進行・転移性乳癌に対しての報告は少なく，臨床病期・病理学的因子・妊娠週数・出産予定日の評価と共に患者の社会心理学的背景を理解し，多職種による支援やカウンセリングを用いて妊娠継続するかどうかも含め患者と共に方針を決定していくことが肝要である[14]．

1）妊娠期の化学療法

流産率の増加と胎児奇形の増加から妊娠初期での使用は避けることが一般的である．妊娠中期以降では影響は少なく比較的安全に行えると考えられており，CAF療法とAC療法がもっとも施行経験の報告が多いレジメンとなる．妊娠中に化学療法施行したときの出生時の先天異常は，その場合約1.3％と通常と変わらないと考えられている[15~22]．前投薬として5-HT3受容体拮抗剤であるオンダンセトロン，ベンゾジアゼピン系抗不安薬であるロラゼパム，デキサメタゾンは安全に使用可能である．化学療法施行中は妊娠週数に比して成長が遅れることもあることから可能な限り胎児モニタリングを行い出産予定日の検討をすることが重要である．また出産時の血液凝固系の合併症を避けるために35週以降または出産予定日の3週前には投薬は中止すべきであると考えられている[14]．タキサン系抗癌剤の妊娠中の使用報告はまだ数少なく安全性が不明と考えられガイドラインでは推奨されていないが，安全に行えるという



資料：独立行政法人国立がん研究センターがん対策情報センター
Source：Center for Cancer Control and Information Services, National Cancer Center, Japan

図2 乳癌年齢階級別罹患率の推移（1985年，2005年）
（独立行政法人国立がん研究センターがん対策情報センター HP http://ganjoho.jp/pro/statistics/gdball.html?21%2%1より引用・改変（Accessed 2013-01-18））

報告もある[23~28]．トラスツマブも安全性の観点から出産後に使用すべきであると考えられており同様であるが[29~31]，両者とも妊娠期の安全使用について議論の余地があると考えられている．

2）妊娠期の集学的治療

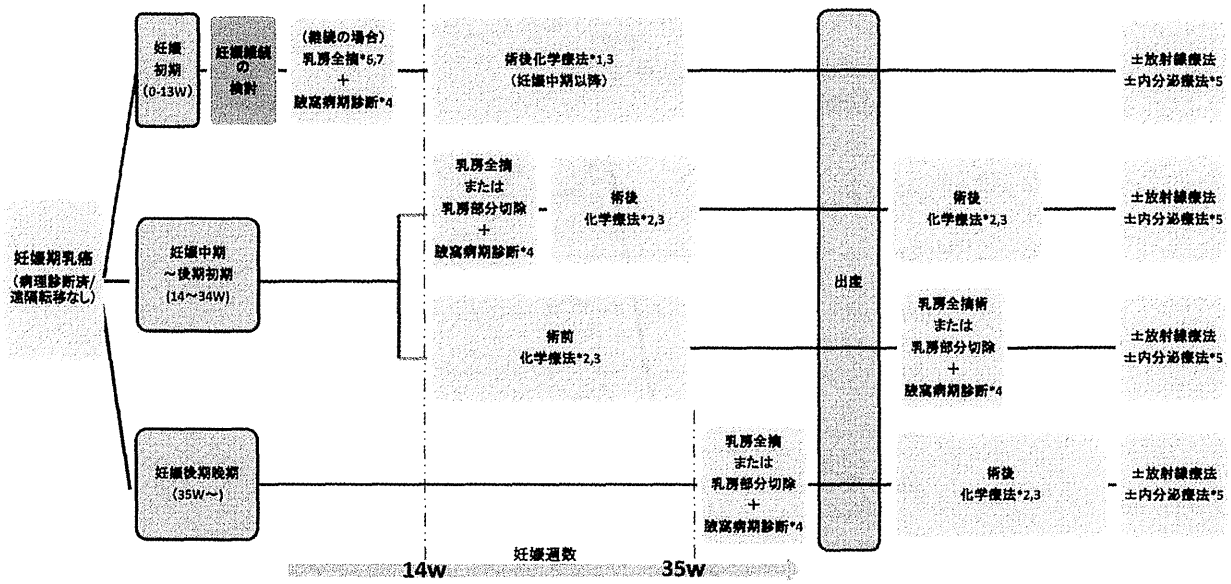
全身麻酔は比較的安全であることから手術は可能であるが，流産・早産の可能性は念頭に置かなければならない．一方で妊娠中の放射線療法・内分泌療法は禁忌となる．これらのことから臨床病期と治療開始時の妊娠週数を検討し治療方針を決定することがもっとも重要となる．NCCNのガイドラインを時系列に重点を置き一部改変したものを示す（**図3**）．

（1）1st trimester（0～13週）

妊娠継続について慎重に検討したのち，継続の場合は化学療法が選択できない時期であることから外科的切除を行い，妊娠中期（13週以降）に入ってから化学療法を施行することが勧められている．外科的切除を考慮する場合，放射線療法の遅れがない場合は乳房切除術に代わり乳房部分切除も選択可能と考えられているが，妊娠初期の場合は放射線療法開始までに時間が開くことから部分切除は術式として推奨されていない．

（2）2nd trimester（14週～28週）およびEarly 3rd trimester（29週～34週）

臨床病期により手術先行か術前化学療法施行か2つの選択肢があるが，手術先行の場合，術後補助化学療法施行の際は途中で出産が入ることが多い．この場合出産予定の3週前または妊娠35週には投薬を



*1 化学療法は妊娠初期には施行すべきではなく，中期以降に施行すべきである．
*2 中期以降の化学療法施行時，出産予定に合わせ産科・乳腺治療医が相談し休薬・再開時期を慎重に検討すべきである．また化学療法施行に伴い，週数に比して成長がやや遅れる可能性も検討すべきである．
*3 妊娠中施行する化学療法では，CAF6サイクルがもっとも経験されているレジメンである．Taxianeについてはまだ安全性についてのデータが不十分である．またトラスツマブは禁忌である．
*4 妊娠中の腋窩病期診断でセンチネルリンパ節生検を施行する場合，色素法は禁忌であり，RI法単独が勧められる．
*5 放射線療法・内分泌療法は妊娠中は行われるべきではない．
*6 放射線療法を出産後まで待てない場合，乳房全摘が適応となる．
*7 妊娠初期の手術については妊娠週数に応じて麻酔科・産科と相談の上可否を検討するべきである．

図3 妊娠期乳癌の治療の流れ
（NCCN Guideline ver3.2012 Breast Cancer During Pregnancy より一部改変）

中止，また産後すぐには治療再開できないことから，出産前後の化学療法投与間隔が開くことが予想される．

（3）Late 3rd trimester（35週以降）

出産直前の化学療法は血液凝固系合併症の懸念があることから，この時期では手術が選択される．妊娠晩期での全身麻酔に伴う早産のリスクを念頭にいれ，産科・小児科・麻酔科の協力のもと準備して臨む必要がある．

いずれも出産後は通常乳癌と同様に集学的治療を行うことが重要である．産後の化学療法では，母乳への薬物移行の問題，部分切除症例では患側の乳腺炎のリスク，腋窩隔清症例では上肢浮腫に伴う蜂窩織炎のリスク，新生児を抱えての治療による精神負荷の増大などさまざまな問題を念頭に置き，多職種で対応できる体制を組む必要がある．

2．乳癌罹患患者の妊娠 —サバイバーの挙児希望—

1）乳癌罹患後の妊娠出産のリスクについて

かつては妊娠が乳癌の予後に及ぼす影響の恐れや過去の治療による卵子への影響の懸念から，乳癌罹患後の妊娠出産は避けられていた．しかし近年では多くの後方視的臨床研究から，ホルモン陽性乳癌を含め乳癌罹患患者の妊娠出産は乳癌の予後に影響しないという考え方が浸透しつつあり，今後サバイバーの妊娠出産に関する需要は高まると考えられる[32~34]．今までは妊孕性保護について議論されることは少なかったが，近年欧米では生殖年齢で薬物療法を施行されるすべての癌患者にとって検討されるべ

きという認識が広がり指針が示されている[35~37]．国内では乳癌専門医へのアンケート調査により乳腺治療医の知識と妊孕性保護への積極的姿勢が情報提供行動と関連することが示唆されており，治療医により患者の持つ情報や選択肢に差があることが推察されている[38]．今後患者の需要が多様化するなかで，私たち癌治療医と生殖医療専門家・産婦人科医の相互理解と協力体制の構築が急務であると考えている．

2）化学療法や内分泌療法に伴う卵巣機能障害

閉経前の乳癌患者に化学療法を施行したとき，多くの場合2～3カ月後に治療関連性無月経が認められる．治療終了後の月経再開は年齢が40歳以上で困難であると考えられているが，筆者らの検討では年齢に加え，化学療法の治療期間と化学療法後の内分泌療法施行の有無も月経再開の有無に関連することが示唆された[39~41]．一方，内分泌療法施行例ではタモキシフェンの催奇性による5年間の避妊が必要である．治療開始前に治療終了後の自然妊娠の可能性を予測することは理想であるが，現段階では困難である．一方で生殖医療の現場では卵巣機能は年齢に必ずしも相関しないと考えられており，将来の出産を希望している患者にとって，乳癌薬物療法は年齢に寄らずライフプランの変更を余儀なくされる可能性を含んでいるという認識が重要であり[5]，これらをあらかじめ患者に説明しメリット・デメリットを検討し治療方針を決定しなくてはならないと考えている．

3）乳癌治療医と生殖医療専門医による支援システム ― Oncofertility とは―

ここでは将来癌を克服して妊娠出産を望む患者に現段階で考えられる選択肢について述べる．治療終了後の自然妊娠の可能性を完全に予測することはできないが，治療開始前から ART のサポートを得ておくことで妊娠出産の可能性を広げることができる．具体的には薬物療法開始前に採卵し受精卵，未受精卵あるいは卵巣組織を凍結保存しておき，治療が落ち着いたら人工授精により妊娠するという方法である．この方法を選択するためには，治療開始前に乳癌の臨床病期や病理学的因子による再発リスク，薬物療法による risk reduction benefit とそのスケジュール，乳癌薬物療法開始前の卵巣機能および妊孕性の評価と予測される治療終了後の卵巣機能について，十分なアセスメントと情報提供が必要である．また患者の社会心理学的背景（パートナーの有無・家庭環境・経済的な問題）など条件も，重要な因子と考えられる．生殖医療を乳癌初回治療に組み込んだ場合，筆者らが考えている治療の流れを示す（図4）．

妊孕性保持支援において，乳癌治療医と生殖医療専門医の円滑な連携が必要と考えられたため，筆者らは日本生殖医学会に協力を依頼し生殖医療専門医に対し乳癌患者の生殖補助医療についての意識・行動についてのアンケート調査を行った．その結果排卵誘発剤を用いた場合の乳癌の予後への影響についてデータが数少ないことが問題としてあがったが，採卵や生殖補助を行うことは可能であるという見解を得た．また，乳癌治療医と生殖医療医の一定のコンセンサスや，施設間のネットワークの構築，施設内の支援体制の整備が必要であるという意見も多くあがった．日本生殖医学会のホームページには，本アンケート調査に基づいて筆者らが作成した乳癌患者の生殖補助医療への協力に賛同した医療機関の一覧が掲載されている[42]．

おわりに

患者を理解し癌治療医として治療を練ることはもっとも重要であるが容易なことではない．とくに個々の妊娠と乳癌の問題を検討するためには患者の価値観・人生観の問題でもあることから，方針の決定には相応の時間が必要となる．現在筆者らの研究班では乳癌患者の将来の妊娠出産についてのポイントをまとめた患者向け情報提供リーフレットと，癌治療医や生殖専門医向けのガイドラインの作成に向け活動している．リーフレットやガイドラインにより癌治療医から患者への情報提供が簡便になり，日常臨床で取り入れやすくなるのではないかと考える．また妊娠期乳癌や乳癌罹患後の妊娠についてまだ不明な点が多く，それらを解決するためにはこの2つについてのデータベース構築も重要であると考え

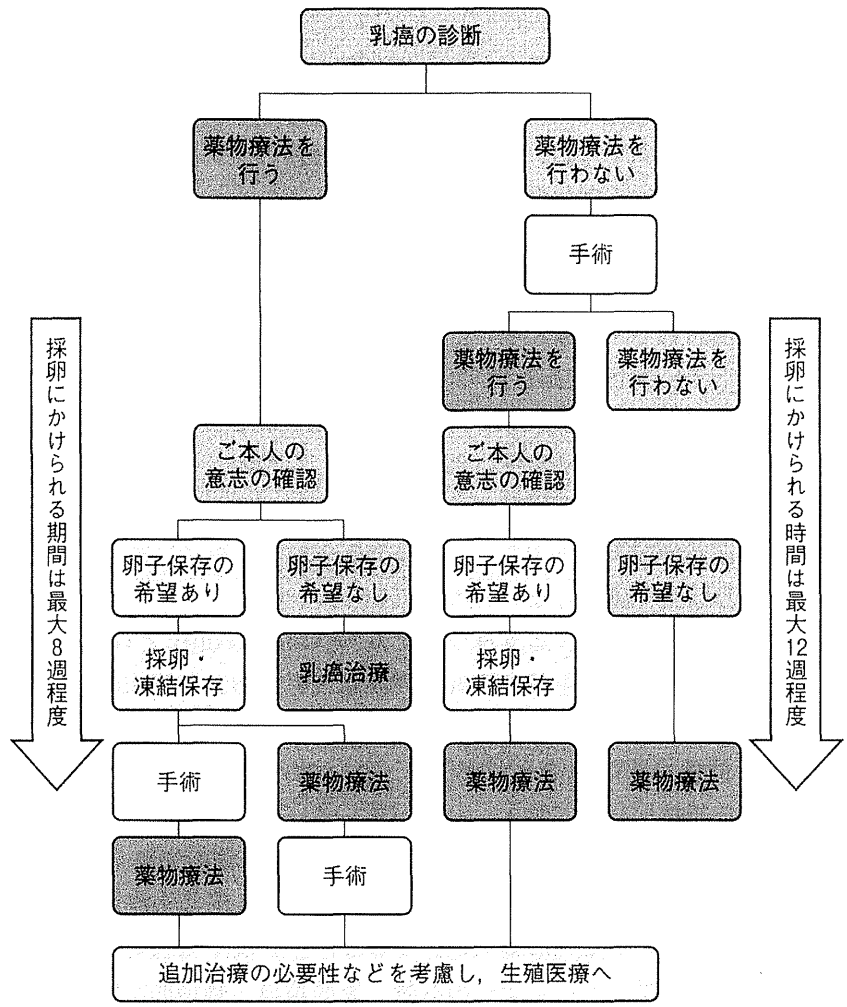


図4　乳癌治療と生殖医療の流れ

られる．アメリカではすでにこれらのデータベース構築に向け始動しており，妊娠期乳癌については患者のネットワークが作られさまざまな情報提供が為されている[43~45]．国内でも妊娠・出産を希望する乳癌患者と癌治療医・生殖医療専門医に役立つツールを作成し発信していきたい．

文　献

1）Steinberg C：Can Women Save Japan (and Asia Too)? FINANCE & DEVELOPMENT 349, 2012
2）内閣府：平成18年度国民生活白書・多様な可能性に挑める社会に向けて，第2章　女性のライフサイクルと就業 第2節　女性の継続就業を妨げる壁，第3節　女性の再就職を妨げる壁．http://www.caa.go.jp/seikatsu/whitepaper/h18/01_honpen/index.html (Accessed 2013-01-18)
3）内閣府：平成17年度版国民生活白書「子育て世代の意識と生活」第1章第1節　晩婚化・非婚化と出生力．http://www5.cao.go.jp/seikatsu/whitepaper/h17/01_honpen/index.html (Accessed 2013-01-18)
4）内閣府：平成17年度国民生活白書「子育て世代の意識と生活」第1章第1節コラム　不妊．http://www5.cao.go.jp/seikatsu/whitepaper/h17/01_honpen/index.html (Accessed 2013-01-18)
5）浅田義正：不妊治療施設における患者教育と説明について．日本産婦人科医会報　医療と医業 64：6, 12, 2012
6）独立法人国立がん研究センターがん対策情報センター：がん情報サービス．http://ganjoho.jp/public/index.html (Accessed 2013-01-18)
7）Letourneau JM, Smith JF, B. Ebbel EE, et al：Racial, Socioeconomic, and Demographic Disparities in Access to Fertility Preservation in Young Women Diagnosed With Cancer. *Cancer* 118 (18)：4579-4588, 2012

8) Smith LH, Dalrymple JL, Leiserowitz GS, et al : Obstetrical deliveries associated with maternal malignancy in California, 1992 through 1997. *Am J Obstet Gynecol* 184 (7) : 1504-1513, 2011
9) Middleton JP, Amin M, Gwyn K : Breast carcinoma in pregnant women : assesment of clinicopathologic and immunohistochemical features. *Cancer* 98 : 1055-1060, 2003
10) Zemlickis D, Lishner M, Degendorfer P, et al : Maternal and fetal outcome after breast cancer in pregnancy. *Am J Obstet Gynecol* 166 (3) : 781-787, 1992
11) Ishida T, Yokoe T, Kasumi F, et al : Clinicopathologic characteristics and prognosis of breast cancer patients associated with pregnancy and lactation : analysis of case-control study in Japan. *Jpn J Cancer Res* 83 (11) : 1143-1149, 1992
12) Lethaby AE, O'Neil MA, Mason BH : Overall survival from breast cancer in women pregnant or lactating at or after diagnosis. Auckland Breast Cancer Study Group. *Int J Cancer* 67 (6) : 751-755, 1996
13) Murphy CG, Mallam D, Steun S, et al : Current or recent pregnancy is associated with adverse pathologic features but not impaired survival in early breast cancer. *Cancer* 118 (13) : 3254-3549, 2012
14) NCCN : NCCN Guideline version 3.2012, Breast Cancer During Pregnancy.
15) Loibl S, Han SN, von Minckwitz G, et al : Treatment of breast cancer during pregnancy : an observational study. *Lancet Oncol* 13 (9) : 887-896, 2012
16) Sutcliffe SB SB : Treatment of neoplastic disease during pregnancy : maternal and fetal effects. *Clin Invest Med* 8 (4) : 333-228, 1985
17) Doll DC, Ringenberg QS, Yarbro JW : Antineoplastic agents and pregnancy. *Semin Oncol* 16 (5) : 337-346, 1989
18) Ebert U, Loffler H, Kirch W : Cytotoxic therapy and pregnancy. *Pharmacol Ther* 74 (2) : 207-220, 1997
19) Hahn KM, Johonson PH, Gordon N, et al : Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. *Cancer* 107 (6) : 1219, 2006
20) Ring AE, Smith IE, Jones A, et al : Chemotherapy for breast cancer during pregnancy : an 18-year experience from five London teaching hospitals. *J Clin Oncol* 23 (18) : 4192-4197, 2005
21) Germann N, Goffinet F, Goldwasser F : Anthracycline during pregnancy : embryo-fetal outcome in 160 patients. *Ann Oncol* 15 : 146-150, 2004
22) Johnson PH, Gwyn K, Gordon N, et al : The treatment of pregnant women with breast cancer and the outcomes of the children exposed to chemotherapy in utero. Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings 23 (16S) (June 1 Supplement), 2005 : 540, 2005
23) Gainford MC, Clemons M : Breast Cancer in pregnancy : are taxanes safe? *Clinical Oncol* 159 (18) : 2006, 2006
24) Garcia-Manero M, Royo MP, Espinos J, et al : Pregnancy associated breast cancer. *Eur J Surg Oncol* 35 : 215-218, 2009
25) Gonzalez-Angulo AM, Walters RS, Carpenter RJ, et al : Paclitaxel chemotherapy in a pregnant patient with bilateral breast cancer. *Clin Breast Cancer* 5 : 317-319, 2004
26) Mir O, Berveiller P, Ropert S, et al : Emerging therapeutic options for breast cancer chemotherapy during pregnancy. *Ann Oncol* 19 : 607-613, 2008
27) Berveiller P, Mir O : Taxanes during pregnancy : probably safe, but still to be optimized. *Oncology* 83 (4) : 239-240, 2012
28) Cardonick E, Bhat A, Gilmandyar D : Material and fetal outcomes of taxane chemotherapy in breast and ovarian cancer during pregnancy : case series and review of the literature. *Ann Oncol* 23 (12) : 3016-3023, 2012
29) Bader AA, Schlembach D, Tamussino KF : Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. *Lancet Oncol* 8 : 79-81, 2007
30) Pant S, Landon MB, Blumenfeld M : Treatment of breast cancer with trastuzumab during pregnancy. *J Clin Oncol* 26 : 1567-1569, 2008
31) Witzel ID, Muller V, Harps E : Trastuzumab in pregnancy associated with poor fetal outcome. *Ann Oncol* 19 : 191-192, 2088
32) Azim HA Jr, Kroman N, Paesmans M, et al : Prognostic Impact of Pregnancy After Breast Cancer According to Estrogen Receptor Status : A Multicenter Retrospective Study. *J Clin Oncol*, Dec10, 2012 [Epub ahead of print]
33) Azim HA Jr, Santoro L, Pavlidis N, et al : Safety of pregnancy following breast cancer diagnosis : a meta-analysis of 14 studies. *Eur J Cancer* 47 (1) : 74-83, 2011
34) Largillier R, Savignoni A, Gligorov J, et al : Prognostic role of pregnancy occurring before or after treatment of early breast cancer patients aged < 35 years : a GET (N) A Working Group analysis. *Cancer* 115 (22) : 5155-5165, 2009
35) L. JK : Breast cancer and fertility. *Curr Treat Options Oncol* 13 (2) : 137-145, 2012
36) Lee SJ, Schover LR, Partridge AH, et al : American Society of Clinical Oncology recommendations on fertility preservation

in cancer patients. *J Clin Oncol* 24 (18) : 2917-2931, 2006
37) ISFP Practice Committee : Recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer. *J Assist Reprod Genet* 29 (6) : 465-468, 2012
38) Shimizu C, Bando H, Kato T, et al : Physicians' knowledge, attitude, and behavior regarding fertility issues for young breast cancer patients : a national survey for breast care specialists. *Breast Cancer*, 2012 Jan 24 [Epub ahead of print]
39) Bines J, Oleske DM, Cobleigh MA : Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J Clin Oncol* 14 (5) : 1719-1729, 1996
40) Pagani O, O'Neill A, Castiglione M : Prognostic impact of amenorrhoea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement. *Eur J Cancer* 34 (5) : 632-640, 1998
41) Tamura N, Kato T, Shimizu C : Predictive factors of adjuvant therapy-related amenorrhea for patients with breast cancer. Breast Cancer Symposium 2011, Abstract 217
42) 日本生殖医学会ホームページ．「乳がん患者に対する受精卵または未受精卵の凍結保存の受け入れが可能な施設」の一覧について．http://www.jsrm.or.jp/announce/013.html (Accessed 2013-01-18)
43) The pregnant with cancer network, Hope for two. http://www.pregnantwithcancer.org/ (Accessed 2013-01-18)
44) The Oncofertility Consortium, Pregnancy & Cancer Registry. http://oncofertility.northwestern.edu/pregnancy-cancer-registry (Accessed 2013-01-18)
45) University HEalth Care, Cancer And Pregnancy. http://www.cooperhealth.org/departments-programs/cancer-and-pregnancy (Accessed 2013-01-18)

■ 原 著 ■

若年性乳癌術後の乳房定期検査の実態

—多施設アンケート結果より—

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原著

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若年性乳癌術後の乳房定期検査の実態
—多施設アンケート結果より—

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The Follow-up Regimens Received by Young Breast Cancer Patients after Surgery in Japan : A Multicenter Questionnaire : Ogiya A[*1], Takahashi K[*1], Tokunaga E[*2], Fukuuchi A[*3], Masuda N[*4] and Ohno S[*5] ([*1]Department of Breast Surgery, Shizuoka Cancer Center Hospital, [*2]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, [*3]Department of Breast Endocrine Surgery, Mitsui Memorial Hospital, [*4]Department of Surgery, Osaka National Hospital, [*5]Department of Breast Surgery, National Kyushu Cancer Center)

The follow-up regimens received by young breast cancer patients after surgery at different hospitals are unknown. To investigate this issue, a questionnaire was sent to certified breast cancer hospitals under the relevant committee of the Ministry of Health, Labour and Welfare (collection rate, 69%). Sixteen percent of the hospitals perform original follow-up regimens for young patients, with performance rates of clinical examination, mammography, and ultrasonography being 98, 93, and 82%, respectively. Clinical examinations were performed less than six months apart in 79% of respondents, yearly mammography was performed in 85%, and yearly ultrasonography was performed in 53%. About 80% of the hospitals stopped follow-up within 10 years. For young breast cancer patients in Japanese hospitals, follow-up mammography is performed regularly, and follow-up ultrasonography is often performed. It remains necessary to assess the efficacy of ultrasonography for follow-up and to devise a screening system for surgically treated patients.

Key words : Breast cancer, Young patient, Screening
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はじめに

術後乳房定期検査の指針が乳癌診療ガイドラインに示されているが[1]，日本の各施設における術後乳房定期検査の現状は把握されていない．

平成22年度がん研究開発費による班研究「若年乳癌患者のサバイバーシップ支援プログラムの構築に関する研究」班（班長：九州がんセンター大野真司）で，若年性乳癌の術後フォローアップ方法を検討している．今回班研究の中で，若年性乳癌に対する術後乳房定期検査の日本の現状を把握することを目的に，アンケート調査を施行した．

1．対象と方法

厚生労働省班研究の中で日本乳癌学会認定402施設にアンケート用紙を郵送しファックスでの回答を依頼した．278施設から回答を得た（回収率69%）．アンケート用紙はA4サイズの1枚とし①若年性乳癌と通常の乳癌を分けて術後乳房検査を行っているか，②術後の視触診・マンモグラフィ（MMG）・超音波検査（US）・その他の検査

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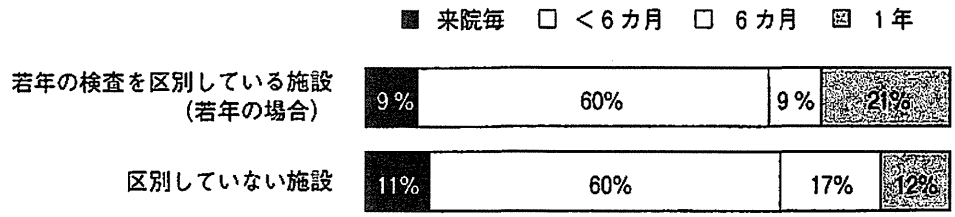

図7　術後視触診の施行間隔

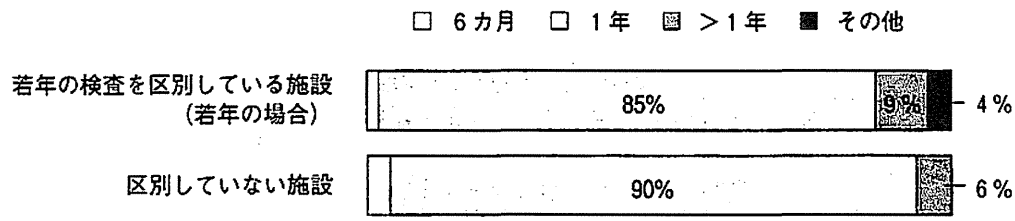

図8　術後マンモグラフィの施行間隔

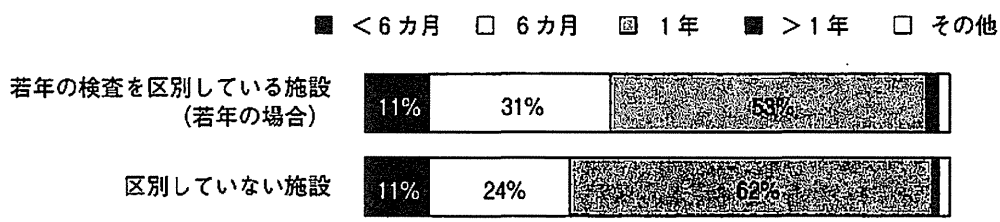

図9　術後超音波検査の施行間隔

れたので今回の検討からは除外した．検査施行間隔については視触診は若年を区別しているかしていないかにかかわらず6カ月以下が多く認められ(図7)，MMGは多くの施設が1年間隔であった(図8)．USも1年間隔がもっとも多く認められたが，若年の検査を区別している施設では42%が6カ月以下と短い間隔でUSを施行していた（図9)．視触診，MMG，USの定期検査期間は術後10年までが約80%を占めていたが，若年の検査を区別している施設では無期限の割合が若年を区別していない施設よりも高い傾向にあった（図10)．手術件数によるUSの実施割合に差は認められず，手術件数が50件未満の施設ではUSの施行間隔は6カ月以下が24%であったのに対し50件以上では40%あり，手術件数が多いほど短期間にUSが施行されていた．

3．考　察

若年性乳癌に限らず日本の術後乳房定期検査の現状を調査した報告はいまだない．今回の調査により，乳腺の診療に日常携わっている日本乳癌学会認定施設の術後乳房定期検査の現状が明らかとなった．

調査はアンケート形式を用い，アンケート用紙はA4サイズの1枚とし短時間で回答可能なデザインとした結果，69%の高い回収率を得ることができた．

文献検索した範囲内では若年性乳癌に対する術後乳房定期検査について検討を行っている報告は認められなかったが，日本の乳癌認定施設では16%が若年性を区別して独自に術後乳房定期検査を施行していることが分かった．

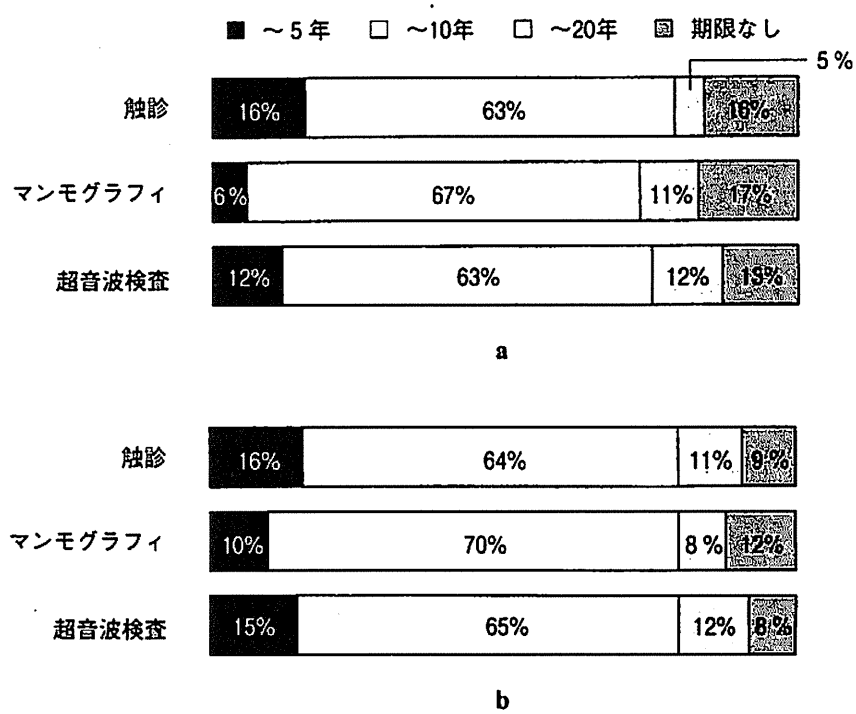

図10 各術後乳房検査の施行期間
a：若年の検査を区別している施設（若年の場合）
b：区別していない施設

術後乳房定期検査の目的は治療可能な局所再発および対側乳癌を早期に発見することである[1,2]．日本の乳癌診療ガイドラインでは術後乳房定期検査として視触診を推奨グレードB，MMGを推奨グレードAと位置づけている[1]．現在諸外国でも一般的に行われている術後乳房定期検査はこの2つであるが，各検査の施行間隔や施行期間については世界各国のガイドラインで異なっている[3,4]．The National Institute for Clinical Excellenceは通院頻度に関して明記がなくMMGは術後5年までは年1回行いその後はスクリーニング施設で行うことを推奨している[2]．日本の乳癌診療ガイドラインが準拠したThe American Society of Clinical Oncologyは最初の5年間は3から6カ月毎に来院し，その後は年に1回10年までの通院と年1回のMMGを推奨している[5]．各国のガイドラインにばらつきがあるのは，予後に関与した適切な術後定期検査の施行間隔や施行期間を決定づける十分なランダム化比較試験がいまだ存在しないためである[1,3]．

若年者のMMGの乳腺濃度は乳癌の検出率が低下する高濃度から不均一高濃度乳腺の割合が高いが[6,7]，若年者に対しても93%の高い割合で術後乳房定期検査にMMGが施行されていた．施行間隔は乳癌診療ガイドラインで示されている1年間隔が85%を占めた．術後MMGの施行間隔をEuropean Society for Medical Oncologyのガイドラインでは閉経状況で分けており，閉経前では年1回，閉経後では1～2年間隔を推奨している[8]．乳癌診療ガイドラインではMMGは術後乳房定期検査として推奨グレードAだが一般検診のような年齢を考慮した記載はない．一般検診では40歳未満に対するMMGは罹患率の低さと診断精度の低さから推奨されていない[1]．しかし術後の場合，乳癌ハイリスクや再発発見の観点から若年でも定期MMGが容認されているのが現状であろう．

術後乳房定期検査のUSについては乳癌診療ガイドラインでまったく言及されていない[1]．USの有用性を検証した研究がないためである．しかし日本の多施設でUSが術後乳房定期検査として施行されているのは，日本の乳腺医が再発や対側

の小病変の発見にUSが有用だと考えていることの表れであると思われる．ただし被曝がないこと，外来で簡便に施行できるため安易に行われている可能性もある．スクリーニングUSの有用性について，乳癌診断にUSをいち早く広く取り入れている日本発の客観的なデータ（Japan Strategic Anti-Cancer Randomized Trial：J-START[9]）の結果が望まれる．

術後乳房定期検査の施行期間は若年性を区別している施設では各検査とも10年以下で終了が8割を占めた．20代の若年性乳癌患者を考えると術後10年時の年齢は30代であり，一般乳癌検診が始まる40歳以下である．このため術後10年を過ぎると検診を受診しない期間が生じていることになる．若年性乳癌は乳癌ハイリスクであり，遺伝性乳癌・卵巣癌症候群（Hereditary Breast and Ovarian Cancer：HBOC）の可能性もある群である．術後定期的な検診を継続して受けることが望まれる群であり，今後はMRIを含めた定期検診や，遺伝カウンセリングも考慮した術後乳房検診のあり方も検討する必要があると思われる[10]．

術後10年後に一般検診へ回った場合，検診を受け入れる側は乳癌術後患者の片側のみのMMGや乳房部分切除後のMMGを読影することになるが，検診初年度でも比較読影ができるように検診を受け入れる側と治療施設との連携が望まれる．

今回の調査は日本の各施設における若年性乳癌の術後乳房定期検査の現状を明らかにすることに主眼を置いた．この現状が適切か否かを判断するには客観的なエビデンスが得にくい分野ではあるが，今後若年性乳癌が術後何年にどの検査で乳房内再発もしくは対側乳癌が発見され，予後はどうであったかについての検討は必要である．

結　語

日本の若年性乳癌術後の乳房定期検査の現状が本アンケート調査により明らかとなった．USの有用性の検証と術後10年以降の検診の受け入れ体制の構築が望まれる．

今回の結果内容の一部は一般女性向けに書き換え，班研究が作成したホームページ http//www.jakunen.com/ で公開されている．

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文　献

1）日本乳癌学会：科学的根拠に基づく乳癌診療ガイドライン2　疫学・診断編　2011年版．金原出版，東京，2011
2）National Institute for Clinical Excellence：Early and locally advanced breast cancer：diagnosis and treatment. National Collaborating Center for Cancer, Wales, 2009
3）Montgomery DA, Krupa K, Cooke TG：Alternative methods of follow up in breast cancer：a systematic review of the literature. *Br J Cancer* 96：1625-1632, 2007
4）Montgomery DA, Krupa K, Cooke TG：Follow-up in breast cancer：does routine clinical examination improve outcome? A systematic review of the literature. *Br Journal Cancer* 97：1632-1641, 2007
5）Khatcheressian JL, Wolff AC, Smith TJ, et al：American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol* 24：5091-5097, 2006
6）森本忠興，長尾妙子，岡崎憲二，他：乳癌検診の現状．外科治療 101：637-645，2009
7）大貫幸二，宇佐美伸：超音波併用MMG検診　同時併用検診の意義と課題．映像情報 Medical 41：1293-1296，2009
8）Kataja V, Castiglione M, and on behalf of the ESMO Guidelines Working Group：Primary breast cancer：ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 20 (Supplement 4), 2009
9）Ohuchi N, Ishida T, Kawai M, et al：Randomized controlled trial on effectiveness of ultrasonography screening for breast cancer in women aged 40-49 (J-START)：research design. *Jpn J Clin Oncol* 41：275-277. Epub 2011
10）Narod SA：Screening of women at high risk for breast cancer. *Prev Med* 53：127-130. Epub 2011

Efficacy of goserelin plus anastrozole in premenopausal women with advanced or recurrent breast cancer refractory to an LH-RH analogue with tamoxifen: Results of the JMTO BC08-01 phase II trial

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Abstract. The aim of the present study was to assess the efficacy and tolerability of a luteinizing hormone-releasing hormone (LH-RH) analogue plus an aromatase inhibitor following failure to respond to standard LH-RH analogue plus tamoxifen (TAM) in premenopausal patients. Premenopausal women with estrogen receptor (ER)-positive and/or progesterone-receptor positive, advanced or recurrent breast cancer refractory to an LH-RH analogue plus TAM received goserelin (GOS) in conjunction with anastrozole (ANA). The primary endpoint was the objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR) and safety. Between September 2008 and November 2010, 37 patients were enrolled. Thirty-five patients (94.6%) had ER-positive tumors, and 36 (97.3%) had human epidermal growth factor receptor (HER) 2-negative tumors. Thirty-six (97.3%) had measurable lesions and 1 (2.7%) had only bone metastasis. The ORR was 18.9% [95% confidence interval (CI), 8.0-35.2%], the CBR was 62.2% (95% CI, 44.8-77.5%) and the median PFS was 7.3 months. Eight patients had adverse drug reactions but none resulted in discontinuation of treatment. GOS plus ANA is a safe effective treatment for premenopausal women with hormone receptor-positive, recurrent or advanced breast cancer. The treatment may become viable treatment in the future, particularly when TAM is ineffective or contraindicated. Further studies and discussion are warranted.

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Key words: aromatase inhibitor, breast cancer, luteinizing hormone-releasing hormone analogue, premenopausal patient, tamoxifen

Introduction

Approximately 70% of all cases of breast cancer are hormone receptor-positive. Endocrine therapy is generally used for adjuvant treatment and the management of recurrence in hormone-sensitive breast cancer. Ovarian suppression induced surgically or with a luteinizing-hormone-releasing hormone (LH-RH) analogue as a postoperative adjuvant therapy can prevent recurrence and prolong survival in premenopausal women with breast cancer. The effectiveness of these treatments is comparable to that of chemotherapy (1,2). In premenopausal women, estrogen is synthesized primarily by the ovaries, and high estrogen concentrations are maintained in the blood. After menopause, the decline in ovarian function is accompanied by a significant decrease in estrogen concentrations in the blood, although levels remain high enough to stimulate the proliferation of breast cancer cells. Estrogen in postmenopausal patients is largely produced in peripheral adipose tissue and in cancer cells, and the peripheral aromatase is not under gonadotropin regulation (3). Therefore, aromatase inhibitors are used as standard treatment in postmenopausal

women with breast cancer following the cessation of ovarian function. Particularly in patients with recurrent or metastatic breast cancer, the major treatment objectives are to maintain or improve the quality of life (QOL) and to prolong survival. Treatment should therefore be initiated with endocrine therapy.

Endocrine therapy basically involves sequential administration of single agents. However, the combined use of an LH-RH analogue and tamoxifen (TAM) is superior to monotherapy (4) and is, therefore, the treatment of choice for premenopausal women with advanced or recurrent breast cancer. However, when the disease is resistant to combination therapy involving LH-RH analogue and TAM, alternative regimens for endocrine therapy are currently unavailable, with the exception of synthetic progesterone agents (medroxyprogesterone acetate). A number of patients must therefore receive chemotherapy. Consequently, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend that premenopausal women with advanced or recurrent breast cancer undergo ovarian ablation or suppression and then receive treatment similar to that recommended for postmenopausal women. The above mentioned guidelines recommend that premenopausal breast cancer patients undergo a combination treatment that includes an LH-RH analogue and an aromatase inhibitor. However, few studies support this treatment regime for premenopausal patients. Forward *et al* (5) studied goserelin (GOS) plus anastrozole (ANA) as a second-line endocrine therapy in 16 premenopausal women with advanced breast cancer who had previously received an LH-RH analogue plus TAM. After 6 months of treatment, 1 patient had partial response (PR), 9 had stable disease (SD) and 2 had a biochemical response. The clinical benefit rate was 75%. Serum estradiol levels were measured during treatment. Introduction of GOS and TAM reduced mean estradiol levels by approximately 89%. Substitution of TAM with ANA further decreased estradiol levels by 76%. This represents a marked decrease compared with the level during treatment using GOS and TAM.

These results suggest that combination therapy with an LH-RH analogue and an aromatase inhibitor is a viable treatment option for premenopausal women with breast cancer. To confirm this hypothesis, we studied the response rate to an LH-RH analogue plus ANA in women who failed to respond to an LH-RH analogue plus TAM. Progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR) and safety were also assessed.

Patients and methods

Study design. This open-label, single-arm, multi-center, phase II study (registration no. UMIN000001217) was conducted to assess the efficacy and safety profile of an LH-RH analogue and an aromatase inhibitor combination therapy in patients with TAM-refractory, ER-positive, premenopausal metastatic breast cancer in Japan between September 2008 and February 2012. The following treatment was initiated within 4 weeks after enrollment. Anastrozole (Arimidex) 1-mg tablets were administered orally once daily. A 3.6-mg depot of GOS acetate (Zoladex) was injected subcutaneously into the lower abdomen once every 4 weeks (28 days). Treatment was continued until the development of progressive disease (PD) or unacceptable adverse events.

This study was conducted in accordance with the Declaration of Helsinki, and the Ethical Guidelines for Clinical Studies, July 30, 2003 (Amended December 28, 2004) by the Ministry of Health, Labor and Welfare, Japan. This protocol was approved by JMTO (The Japan-Multinational Trial Organization) Ethics Committee in February 2008 and was also approved by the Ethics Committee of each institution. The local assessment [complete response (CR), PR or prolonged SD of ≥24 weeks] was confirmed independently by two radiologists.

Eligible patients. Eligible patients had to meet all of the following inclusion criteria at study entry: premenopausal women 20-55 years of age (at enrollment); a confirmed diagnosis of metastatic or recurrent breast cancer; measurable lesions [according to Response Evaluation Criteria in Solid Tumors (RECIST)] or assessable bone lesions; refractoriness to previous treatment with an LH-RH analogue plus TAM; compliance with one of the following four conditions: i) recurrence while receiving postoperative therapy with an LH-RH analogue plus TAM; ii) recurrence within 1 year after the completion of at least 2 years of postoperative treatment with an LH-RH analogue plus TAM; iii) recurrence while receiving postoperative treatment with TAM alone after at least 2 years of treatment with an LH-RH analogue plus TAM or recurrence within 1 year after the completion of treatment with TAM, or iv) progressive disease while receiving combination therapy with an LH-RH analogue plus TAM for the management of advanced or recurrent breast cancer; estrogen receptor (ER)- and/or progesterone receptor (PgR)-positive breast cancer (positivity rate ≥10% on immunohistochemical analysis), an Eastern Cooperative Oncology Group performance status of 0 or 1; in patients who were receiving bisphosphonates, measurable lesions in sites other than the bone able to be followed up for antitumor response; with no serious complications; and written informed consent to participate in the study, received directly from the patient.

Patients were excluded from the study if they met any of the following criteria: i) a history of allergy to the study drug or concurrently used drugs; ii) treatment with other antitumor agents after prior therapy (LH-RH analogue plus TAM or LH-RH analogue plus TAM→TAM); iii) continuous treatment with systemic corticosteroids (orally or intravenously); iv) advanced cancer in other organs <5 years after treatment; v) a history of thrombosis, such as deep vein thrombosis or cerebral infarction; vi) a history of serious cardiac disease, such as myocardial infarction, valvular disease, or heart failure; vii) hormone-replacement therapy for climacteric symptoms received for ≤4 weeks at the time of enrollment; viii) women who were pregnant, breast feeding, or possibly (planning to be) pregnant; ix) treatment with antineoplastic agents other than an LH-RH analogue plus ANA, bisphosphonates, or radiotherapy of target lesions scheduled to be received after the start of the study; and x) patients considered unsuitable for the study by the investigator.

Study variables. The variables investigated included age, body-mass index, tumor diameter of the primary lesion, lymph-node metastasis, ER, PgR, human epidermal growth factor receptor (HER) 2 status, sites of metastasis or recurrence, performance

status at enrollment (according to the Eastern Cooperative Oncology Group), the presence or absence of postoperative radiotherapy, and the presence or absence of chemotherapy. Immunohistochemical staining was used to evaluate ER, PgR and HER2. ER and PgR were judged to be positive if the percentage of positive cells was ≥10%. HER2-positivity was defined as 3+ by immunohistochemistry or HER2 amplification by fluorescent *in situ* hybridization (HER2/CEP17 >2.0).

Endpoints. The primary endpoint was the response rate. Tumor shrinkage was evaluated according to the RECIST version 1.0 (6), and response was categorized as CR, PR, SD or PD. Bone lesions are generally considered non-target lesions as they are unmeasurable. However, bone is a common site of metastasis from breast cancer, in which the rate of metastasis is as high as 70-80%. In the present study, bone metastases were considered target lesions for the evaluation of response only in patients who only had bone metastases. The response of bone lesions was evaluated according to the standards of the Japanese Breast Cancer Society (7). If lesions existed in sites other than bone, bone lesions were evaluated as non-target lesions.

Secondary endpoints were PFS, OS, CBR and safety. PFS was defined as the number of days from enrollment to an initial event (disease progression or mortality from any cause, whichever occurred first). CBR was defined as the percentage of patients who had a CR, PR or prolonged SD maintained for at least 24 weeks among all eligible subjects. Safety was evaluated according to the Common Terminology Criteria of Adverse Events (CTCAE), version 3.0 (8).

Statistical analysis. The design of this study was based on a binomial distribution with no planned interim analysis. Assuming a null hypothesis of a 6% ORR and an alternative hypothesis of a 20% ORR, with one-sided type I error = 0.025 and type II error = 0.2, the required sample size was calculated to be 33. The planned sample size was set at 35, with the consideration of ~5% of patients being ineligible.

Exact confidence intervals (95% CI) were calculated for CBR and ORR. PFS and OS were estimated by the Kaplan-Meier method. The incidence of grade 3 or 4 adverse events is shown according to type. If an adverse event of the same type and the same grade developed twice in the same patient, it was counted as one event. Statistical analysis was performed with SAS System Release 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. From September 2008 to November 2010, a total of 37 patients were enrolled in the study. The patients were followed up and outcomes were confirmed in February 2012. Table I shows the demographic characteristics of the 37 patients. The median age was 43.0 years (range, 33-53), and the median body-mass index was 21.6 kg/m^2 (range, 16.9-30.3). The median disease-free interval (DFI) was 58.0 months (range, 0.9-201.3) and 12 patients (42.9%) had longer DFI (>60 months). ER/PgR status was ER+/PgR+ in 27 patients (73.0%), ER+/PgR- in 8 (21.6%) and ER-/PgR+ in 2 (5.4%). HER2 was negative in 36 patients (97.6%). During prior treatment with an LH-RH analogue plus TAM, 26 patients (70.3%) had PD, and 6 (16.2%) had recurrence during postoperative adjuvant therapy; 5 patients (13.5%) had completed the previous course of adjuvant therapy. Previous treatment included radiotherapy in 13 patients (35.1%) and chemotherapy in 20 (54.1%).

Table I. Patient characteristics.

Characteristics (n=37)	Median	Range
Age (years)	43.0	33-53
BMI (kg/m^2)	21.6	16.9-30.3
Disease-free interval (months; 28 recurrent cases)	58.0	0.9-201.3

Characteristics (n=37)	No. of patients	%
ER and PgR status		
ER+ and PgR+	27	73.0
ER+ and PgR-	8	21.6
ER- and PgR+	2	5.4
HER2 status		
Negative	36	97.3
Unknown	1	2.7
Description of previous treatment (LH-RHa + TAM)		
Recurrence during postoperative therapy	6	16.2
Recurrence within 1 year after completing postoperative therapy	1	2.7
Recurrence during continued adjuvant therapy with TAM alone or within 1 year after completion	4	10.8
Disease progression during treatment for advanced or recurrent breast cancer	26	70.3
History of other previous treatments		
Prior radiotherapy	13	35.1
Prior chemotherapy	20	54.1
Presence of metastatic sites (n=37)		
No	6	16.2
Yes	31	83.8
Metastatic sites (n=31)		
Breast	2	6.5
Skin	2	6.5
Lymph nodes	12	38.7
Bone	14	45.2
Lung	9	29.0
Pleura	1	3.2
Liver	9	29.0
Type of treated lesions (n=37)		
Measurable disease	15	40.5
Measurable + bone	21	56.8
Bone only	1	2.7

LH-RHa, luteinizing hormone-releasing hormone analogue; TAM, tamoxifen; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PgR, progesterone receptor.

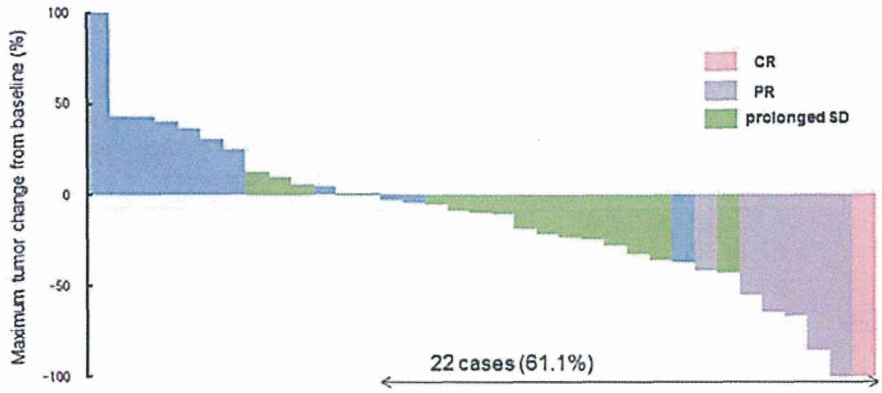

Figure 1. Waterfall plot of maximal change (%) in RECIST-evaluable tumor size from baseline. Thirty-six patients had measurable disease at baseline, and tumor shrinkage was found in 22 patients (61.1%). Of the patients with long-SD, 12 patients (75%) had tumor shrinkage. CR, complete response; PR, partial response; SD, stable disease.

Table II. Objective response rates and clinical benefit rates.

Response	No. of patients	%	95% CI
Complete response	1	2.7	
Partial response	6	16.2	
Objective response	7	18.9	8.0-35.2
Stable disease ≥24 weeks	16	43.2	
Clinical benefit	23	62.2	44.8-77.5
Stable disease <24 weeks	2	5.4	
Progressive disease	11	29.7	
Not evaluable[a]	1	2.7	

[a]Response was not assessable in 1 patient who withdrew her informed consent as she wanted to receive a folk remedy. CI, confidence interval.

Thirty-one patients had distant metastases and 6 had locally advanced disease. The sites of metastasis were bone in 14 patients, lymph nodes in 12, liver in 9, lung in 9, contralateral breast in 2, distant skin in 2 and pleura in 1. Thirty-six patients (97.3%) had measurable disease, 21 (56.8%) of the patients also had bone lesions and 1 had only bone metastasis.

Clinical effectiveness. Clinical effectiveness is summarized in Table II. One patient (2.7%) had a CR, and 6 (16.2%) had PR for a response rate of 18.9% (95% CI, 8.0% to 35.2%; P=0.006 under the null hypothesis of a 6% ORR). Sixteen patients (43.2%) had prolonged SD. The CBR was thus 62.2% (23 patients, 95% CI, 44.8-77.5%). Eleven patients (29.7%) had PD. One patient with a response of not evaluable withdrew her informed consent as she wanted to receive a folk remedy. Fig. 1 shows a waterfall plot of maximal change (%) in RECIST-evaluable tumor size from baseline. Thirty-six patients had measurable disease at baseline, and tumor shrinkage was found in 22 patients (61.1%). Of the patients with prolonged SD, 12 patients (75%) had tumor shrinkage.

Regarding the previous treatment (LH-RH analogue+TAM) status, the ORR of the patients was as follows; 16.7% (1/6) in the recurrence group during postoperative therapy, none (0/1) in the recurrence group within 1 year after completing postoperative therapy, none (0/4) in the recurrence group during continued adjuvant therapy with TAM alone or within 1 year after completion, and 23.1% (6/26) in the disease progression group during treatment for advanced or recurrent breast cancer.

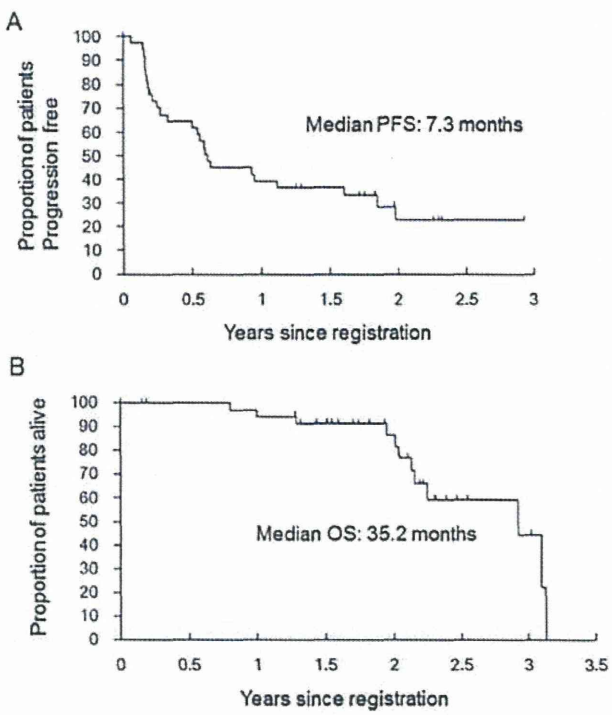

Figure 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) since registration of the 37 enrolled patients. The median PFS and OS were 7.3 and 35.2 months, respectively. New lesions developed in 12 patients, 9 had progression of non-target lesions and 1 had progression of target lesions. Breast cancer was responsible for the 12 deaths.

Patient outcomes. Fig. 2 shows PFS and OS. The median PFS was 7.3 months. New lesions developed in 12 patients, 9 had progression of non-target lesions, and 16 had progression of target lesions. The median OS was 35.2 months. Breast cancer was responsible for the 12 deaths.

Table III. Adverse events and adverse drug reactions.

	Adverse events		Adverse drug reactions	
Event	Grade 1	Grade 2	Grade 1	Grade 2
Hot flashes	9		3	
Joint pain	5	1	1	1
Sweating	7		1	
Laboratory abnormalities[a]	3		3	
Insomnia	3		1	
Pain (limbs)	3			
Arthritis (non-septic)	2			
Fracture[b]		1		
Precordial pain	1		1	
Fatigue	1		1	
Nausea	1		1	

[a]Laboratory abnormalities: abnormal RBC, total cholesterol and ALT values occurred in 1 patient each. [b]Fracture: a fissured fracture occurred after stumbling. There were no grade 3 or 4 adverse events.

Adverse events. Adverse events are shown in Table III. Most adverse events were grade 1. One patient had grade 2 arthralgia and 1 had a grade 2 bone fracture. Adverse drug reactions for which a causal relationship to treatment could not be ruled out are shown. A total of 13 events occurred in 8 patients. With the exception of the grade 2 arthralgia (1 patient), all other events were grade 1. Treatment was not discontinued due to adverse events in any patient. There were no safety issues according to the IDMC.

Discussion

Few confirmatory studies have been performed with aromatase inhibitors in combination with luteinizing hormone-releasing hormone (LH-RH) analogue in premenopausal women with recurrent or advanced breast cancer. Therefore, we studied the clinical effectiveness of creating a goserelin (GOS) and anastrozole (ANA) combination therapy for breast cancer patients who failed to respond to an LH-RH analogue plus tamoxifen (TAM). The response rate was 18.9%, with a clinical benefit rate (CBR) of 62.2%, a median progression-free survival (PFS) of 7.3 months, and a median overall survival (OS) of 35.2 months. On disease progression, second-line treatment options include other types of endocrine therapy for estrogen receptor (ER)-positive breast cancer. Moreover, hormone resistance includes primary (*de novo*) and secondary (acquired) resistance, and the mechanism of resistance between them may differ. It was reported (9) that the patients with secondary resistance responded to the second-line treatment. According to the previous treatment status (LHRH analogue + TAM), the objective response rate (ORR) in the patients (possibly primary resistance) with recurrence during adjuvant therapy or within 1 year after completion was low [total, 9.1% (1/11)]. On the other hand, the ORR was high (23.8%, 6/26) in the patients with disease progression during treatment for advanced or recurrent breast cancer. Although there were several cases with longer disease-free interval (DFI) (possibly secondary resistance), it was difficult to distinguish between primary and secondary hormone resistance in the present study.

Aromatase inhibitors have been shown to increase gonadotropin secretion and to activate ovarian function in premenopausal women (10,11). By contrast, LH-RH analogues inhibit ovarian function and create a postmenopausal hormone environment, facilitating a response to treatment with an aromatase inhibitor. The above mentioned treatment suggests that the combination of aromatase inhibitors with an LH-RH analogue could obtain a complete estrogen blockade by suppressing the ovarian function and the synthesis of peripheral estrogen. In addition, this treatment may produce substantial antitumor activity in premenopausal women (8). Forward *et al* (5) and Carlson *et al* (12) clearly described this hormonal environment.

A meta-analysis comparing an LH-RH analogue alone with an LH-RH analogue plus TAM in premenopausal women with advanced breast cancer showed that the ORR was 29.7 and 38.8%, the median PFS was 5.4 and 8.7 months, and the median OS was 2.5 and 2.9 years, respectively. Outcomes were significantly improved in patients who also received TAM (13). On the basis of these results, an LH-RH analogue plus TAM is currently the standard therapy for premenopausal breast cancer. Regarding the treatment of postmenopausal women with recurrent breast cancer, aromatase inhibitors can be considered a standard endocrine therapy as first-line and second-line treatments (14-18). Aromatase inhibitors appear to be a viable treatment option in combination with an LH-RH analogue given to induce a postmenopausal hormonal environment for premenopausal women with breast cancer.

In the present study, an LH-RH analogue plus an aromatase inhibitor were administered to premenopausal women who failed to respond to an LH-RH analogue plus TAM. In a separate study of first-line treatment with an LH-RH analogue and an aromatase inhibitor in 32 premenopausal women with metastatic breast cancer (12), 1 patient (3.1%) had complete response (CR) and 11 (34.4%) had partial response (PR). All patients had a clinical benefit rate (CBR) of 71.9% and a time to progression of 8.3 months (range, 2.1-63). These results were better than those obtained in our study. The majority of the patients were hormone-naïve (12), while all patients in our study were treated with an LH-RH analogue plus TAM, including the patients who developed recurrence within 1 year after the completion of postoperative treatment with an LH-RH analogue plus TAM. This data supports the recommendations of the NCCN which indicates that the patients who received prior endocrine therapy within 1 year are potential candidates for this treatment.

With regard to the second-line treatment, a retrospective study of GOS plus letrozole (n =16) in premenopausal women with advanced breast cancer (19) reported an ORR of 12.5% (1/16) and a CBR of 56.3% (9/16), which is similar to the results obtained in our study. Furthermore, our prospective study demonstrates the benefits of the GOS plus ANA treatment in premenopausal women refractory to an LH-RH analogue with TAM.

The Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) compared an LH-RH analogue plus TAM with an LH-RH analogue plus an aromatase inhibitor as an adjuvant therapy in premenopausal women with endocrine-responsive breast cancer (20). They found that there was no significant difference between the two endocrine therapy groups and that further observation is necessary. In a retrospective study evaluating the effectiveness of letrozole plus an LH-RH analogue administered concurrently with preoperative chemotherapy and as an adjuvant treatment in premenopausal women with locally advanced ER-positive breast cancer (21), the pathological CR rate, decrease in Ki-67 level, and a higher 5-year disease-free survival rate were significantly improved compared to those in a control group of similar patients who received preoperative chemotherapy followed by TAM plus and an LH-RH analogue after surgery.

The STAGE study by Masuda *et al* (22) was a randomized, double-blind trial of ANA vs. TAM in patients receiving GOS for premenopausal breast cancer in the neoadjuvant setting. The study showed that ANA demonstrated a superior benefit-risk profile compared with TAM as a neoadjuvant treatment in premenopausal women with ER+ breast cancer receiving GOS.

Only 1 patient in our study had a grade 2 adverse drug reaction (arthralgia) and the rest had grade 1 events. No patient discontinued treatment due to adverse events, which were relatively low and were considered symptoms associated with ANA in postmenopausal women. Previous studies have also reported that GOS plus ANA is safe, with no serious adverse events (12).

In conclusion, our results suggest that combination therapy with GOS and ANA is a safe, highly effective, viable treatment for premenopausal women with hormone-sensitive, recurrent or advanced breast cancer. We consider that GOS plus ANA will be recognized as a standard treatment for premenopausal ER-positive recurrent breast cancer, particularly when TAM is contraindicated or ineffective. Further studies and discussion are required to support these results.

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References

1. Jonat W, Kaufmann M, Sauerbrei W, Blamey R, Cuzick J, Namer M, Fogelman I, de Haes JC, de Matteis A, Stewart A, Eiermann W, Szakolczai I, Palmer M, Schumacher M, Geberth M and Lisboa B; Zoladex Early Breast Cancer Research Association Study: Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the 'Zoladex' Early Breast Cancer Research Association study. J Clin Oncol 20: 4628-4635, 2002.
2. Kaufmann M, Jonat W, Blamey R, Cuzick J, Namer M, Fogelman I, de Haes JC, Schumacher M and Sauerbrei W; Zoladex Early Breast Cancer Research Association (ZEBRA) Trialists' Group: Survival analyses from the ZEBRA study: goserelin (Zoladex) versus CMF in premenopausal women with node-positive breast cancer. Eur J Cancer 39: 1711-1717, 2003.
3. Ackerman GE, Smith ME, Mendelson CR, MacDonald PC and Simpson ER: Aromatization of androstenedione by human adipose tissue stromal cells in monolayer culture. J Clin Endocrinol Metab 53: 412-417, 1981.
4. Jonat W, Kaufmann M, Blamey RW, Howell A, Collins JP, Coates A, Eiermann W, Jänicke F, Njordenskold B and Forbes JF: A randomized study to compare the effect of the luteinising hormone releasing hormone (LH-RH) analogue goserelin with or without tamoxifen in pre- and perimenopausal patients with advanced breast cancer. Eur J Cancer 31A: 137-142, 1995.
5. Forward DP, Cheung KL, Jackson L and Robertson JF: Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. Br J Cancer 90: 590-594, 2004.
6. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92: 205-216, 2000.
7. Japan Breast Cancer Society: General Rules for Clinical and Pathological Recording of Breast Cancer. 14th edition. Kanehara Publications, Tokyo, 2000 (In Japanese).
8. National Cancer Institute: Common Terminology Criteria for Adverse Events version 3.0 (CTCAE). http://ctep.cancer.gov.
9. Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, Abadie-Lacourtoisie S, Eymard JC, Debled M, Spaëth D, Legouffe E, Allouache D, El Kouri C and Pujade-Lauraine E: Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. J Clin Oncol 30: 2718-2724, 2012.
10. Smith IE and Dowsett M: Aromatase inhibitors in breast cancer. N Engl J Med 348: 2431-2442, 2003.
11. Smith IE, Dowsett M, Yap YS, Walsh G, Lønning PE, Santen RJ and Hayes D: Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol 24: 2444-2447, 2006.
12. Carlson RW, Theriault R, Schurman CM, Rivera E, Chung CT, Phan SC, Arun B, Dice K, Chiv VY, Green M and Valero V: Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor-positive, metastatic carcinoma of the breast in premenopausal women. J Clin Oncol 28: 3917-3921, 2010.
13. Michaud JB, Jones KL and Buzdar AU: Combination endocrine therapy in the management of breast cancer. Oncologist 6: 538-546, 2001.
14. Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, Steinberg M, Webster A and von Euler M: Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. J Clin Oncol 18: 3758-3767, 2000.
15. Paridaens RJ, Dirix LY, Beex LV, Nooij M, Cameron DA, Cufer T, Piccart MJ, Bogaerts J and Therasse P: Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol 26: 4883-4890, 2008.
16. Mouridsen H, Gershanovich M, Sun Y, Pérez-Carrión R, Boni C, Monnier A, Apffelstaedt J, Smith R, Sleeboom HP, Jänicke F, Pluzanska A, Dank M, Becquart D, Bapsy PP, Salminen E, Snyder R, Lassus M, Verbeek JA, Staffler B, Chaudri-Ross HA and Dugan M: Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol 19: 2596-2606, 2001.
17. Osborne CK, Pippen J, Jones SE, Parker LM, Ellis M, Come S, Gertler SZ, May JT, Burton G, Dimery I, Webster A, Morris C, Elledge R and Buzdar A: Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 20: 3386-3395, 2002.
18. Kaufmann M, Bajetta E, Dirix LY, Fein LE, Jones SE, Zilembo N, Dugardyn JL, Nasurdi C, Mennel RG, Cervek J, Fowst C, Polli A, di Salle E, Arkhipov A, Piscitelli G, Miller LL and Massimini G: Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. J Clin Oncol 18: 1399-1411, 2000.

19. Yao S, Xu B, Li Q, Zhang P, Yuan P, Wang J, Ma F and Fan Y: Goserelin plus letrozole as first- or second-line hormonal treatment in premenopausal patients with advanced breast cancer. Endocr J 58: 509-516, 2011.
20. Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, Pöstlberger S, Menzel C, Jakesz R, Seifert M, Hubalek M, Bjelic-Radisic V, Samonigg H, Tausch C, Eidtmann H, Steger G, Kwasny W, Dubsky P, Fridrik M, Fitzal F, Stierer M, Rücklinger E and Greil R; ABCSG-12 Trial Investigators and Marth C: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 360: 679-691, 2009.
21. Torrisi R, Bagnardi V, Rotmensz N, Scarano E, Iorfida M, Veronesi P, Luini A, Viale G, Santoro A, Colleoni M and Goldhirsch A: Letrozole plus GnRH analogue as preoperative and adjuvant therapy in premenopausal women with ER positive locally advanced breast cancer. Breast Cancer Res Treat 126: 431-441, 2011.
22. Masuda N, Sagara Y, Kinoshita T, Iwata H, Nakamura S, Yanagita Y, Nishimura R, Iwase H, Kamigaki S, Takei H and Noguchi S: Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. Lancet Oncol 13: 345-352, 2012.

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SPECIAL FEATURE

The current status and future perspectives of clinical trial groups in Japan

An overview of the Japan Breast Cancer Research Group (JBCRG) activities

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Abstract The purpose of this article is to describe the current status and future perspectives of the Japan Breast Cancer Research Group (JBCRG). The JBCRG was organized in 2002, with the following purpose: to plan and promote clinical trials and basic research in breast cancer domestically and multilaterally; to conduct research and surveys on domestic and foreign information on medical care for breast cancer and to diffuse and highlight such information; to improve and promote clinical technologies for breast cancer; to act as an intermediary to liaise and strengthen alliances with affiliated organizations; and, to contribute to the public welfare by improving outcomes in breast cancer. The clinical trials are led by doctors/investigators in the JBCRG. And the purpose is to establish standard treatment for patients and provide substantial evidence. The JBCRG implements international collaboration in some researches/studies. As of January 2012, fourteen trials have been closed and nine are open to recruitment.

Keywords Clinical trials · Clinical research · Preoperative systemic therapy · Breast cancer

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Introduction

The incidence of breast cancer in Japan has increased yearly; thus, more attention has been given to breast cancer treatment, among all cancers. In order to save as many breast cancer patients as possible, and to improve their quality of life (QOL), new diagnostic methods, treatments, and prophylaxes for breast cancer should be developed.

The JBCRG shall carry out the following, to serve the aforementioned purpose:

1. Basic and clinical research
2. Collection, analysis, and publication of information
3. Mutual exchange of information
4. Ordinary/extraordinary general meetings
5. Any other affairs required to accomplish the purpose of the JBCRG

The JBCRG has conducted mainly phase II trials to give answers to clinical questions, and now is planning to start phase III ones to achieve clinical approval of new standard therapies. The JBCRG is soliciting donations from organizations and individuals who wish to support its activities. The JBCRG usually manages data quality by central monitoring at data centers including the JBCRG Data Center, which is located in the Kyoto Technoscience Center, Kyoto; however, in some studies such as the SOLE trial, the JBCRG conducted site visits for source document verification.

As of January 2012, 243 doctors from 154 institutes are registered as JBCRG members who are specialists from the breast cancer treating hospitals around Japan. Also, the JBCRG is a member of the Breast International Group (BIG), which is an international breast cancer research group. Tables 1 and 2 summarize the closed and ongoing clinical trials, respectively.

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