eBreast

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Práctica Cáncer de Mama

MANUAL PRÁCTICO PARA LA CONSULTA DE PACIENTES CON CÁNCER DE MAMA

NOVARTIS

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Avales

PARA INFORMACIÓN ADICIONAL, CONSULTAR EL RESTO DE LOS CAPÍTULOS

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PRÓLOGO

eBreast nace como signo de los tiempos.

No es un libro.

No es una app.

Es la respuesta a las nuevas formas de aprender, enseñar y estudiar.

Signo de los tiempos por la importancia y el impacto que tiene el cáncer de mama en nuestra sociedad y en nuestro sistema sanitario.

Signo de los tiempos por la incesante llegada de nuevos profesionales que tienen la gran responsabilidad de cuidar a nuestras pacientes afectas de cáncer de mama y con la necesidad de adquirir un conocimiento riguroso, actualizado y de acceso inmediato, a veces en la propia consulta, para poder ofrecer las mejores opciones que la evidencia científica nos proporciona.

Signo de los tiempos por la forma de enfrentarse a la información. La aparición y expansión de nuevas TIC (Tecnologías de la información y comunicación), algunas de ellas rápidamente absorbidas por las nuevas generaciones, hace preciso adaptarse a ellas.

Signo de los tiempos por el enorme volumen de información que se genera a diario y que hace precisa la intervención de revisores autorizados en cada materia, sobre todo para los clínicos. El fondo de conocimiento médico es inabarcable. Y el conocimiento y el progreso oncológicos son, actualmente, de los más importantes en la medicina moderna: por volumen de publicaciones, recursos que se destinan, impacto social, consecuencias de la enfermedad…

eBreast está dirigido a todos aquellos profesionales que atienden una consulta médica de cáncer de mama, sobre todo a los que se inician en la patología, a los que atienden a estas pacientes de forma más esporádica o simplemente a los que desean mantenerse actualizados. eBreast proporciona una consulta rápida, sencilla y, sobre todo, muy visual e interactiva. Y con este proyecto nos comprometemos a revisar periódicamente los contenidos, actualizando los datos tras los principales acontecimientos científicos del año.

Los coordinadores quisiéramos agradecer el inmenso esfuerzo realizado por todos los autores, así como el apoyo proporcionado por Novartis, y a las sociedades GEICAM, SEOM, SOLTI y a la Universidad CEU Cardenal Herrera por su aval.

No queremos dejar de olvidar el apoyo de nuestras familias y, sobre todo, a LOS/LAS PACIENTES afectos de cáncer de mama, que son el objeto de todos nuestros esfuerzos, estudios y desvelos profesionales y por tanto, los beneficiarios finales de este proyecto, que pretende ser novedoso.

Santiago Olmos Antón **Eduardo Martínez de Dueñas**

ABREVIATURAS

A	Antraciclina
AC	Adriamicina/doxorrubina, ciclofosfamida
ACT	Antraciclina-ciclofosfamida y taxano concurrente
AC-T	Antraciclina-ciclofosfamida y taxano secuencial
AC-D	Adriamicina, ciclofosfamida, docetaxel
AL	Adriamicina Liposomal
ALND	*Axillary lymph node dissection*
AMH	Agente modulador del hueso
ANA	Anastrozol
AO	Ablación ovárica
AP	Adriamicina,paclitaxel
APBI	Radioterapia parcial acelerada
AP-CMF-Q(x)	Adriamicina y paclitaxel-quimioterapia de ciclofosfamida, metotrexato y 5-FU
AP-CMF	Adriamicina y paclitaxel, ciclofosfamida, metotrexato y 5-FU
ASCO	*Sociedad Americana de Clínica Oncología*
AxRT:	*Axillary radiotherapy*
B	Bevacizumab
BAG	Biopsia con aguja gruesa
BAV	Biopsia asistida por vacío
BC	Beneficio clínico
BCS	Supervivencia específica por cáncer de mama
BOADICEA	*Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm*
BSGC	Biopsia selectiva del ganglio centinela
CAF/FAC	Ciclofosfamida, adriamicina y 5-FU
CAFM	Ciclofosfamida, adriamicina, 5-FU y metroxetato
C	Cirugía/Carboplatino
CAP	Capecitabina
CC	Cirugía conservadora
CDDP	Cisplatino
CDI	Carcinoma ductal invasivo

CDIS	Carcinoma ductal *in situ*
CDK	Cinasas dependientes de ciclinas
CEA	Antígeno carcinoembriónico
CEF/FEC	Ciclofosfamida, epirrubicina, 5-FU
CLI	Carcinoma lobulillar infiltrante
CM	Cáncer de mama
CMAJ	*Canadian Medical Association Journal*
CMF	Ciclofosfamida, metotrexato y 5-FU
CMI	Cáncer de mama inflamatorio
CMLA	Cáncer de mama localmente avanzado
CMM	Cáncer de mama metastásico
CMTN	Cáncer de mama triple negativo
cN+	Ganglios linfáticos positivos clínicamente
C-A-CMF	Cirugía-antraciclina-ciclofosfamida, metotrexato y 5-FU
C-AP-CMF	Cirugía-adriamicina, paclitaxel-ciclofosfamida, metotrexato y 5-FU
D	Docetaxel
ddAC	Dosis densas adriamicina y ciclofosfamida
DMO	Densidad mineral ósea
DX	Doxorrubicina
EBCTCG	*Early Breast Cancer Trialists' Collaborative Group*
EC	Epirrubicina, ciclofosfamida
ECG	Electrocardiograma
ECO	Ecografía
ED	Epirrubicina, docetaxel
ESA	Agente estimulador de la eritropoyesis
ESMO	European Society for Medical Oncology
EXE	Exemestano
F	Fulvestrant
FEVI	Fracción de eyección ventricular izquierda
FN	Fiebre neutropénica
GC	Ganglio centinela
GnRH	Hormona liberadora de gonadotropina

G-CSF	Factor estimulante de colonias de granulocitos
TR	Trastuzumab
HD	Altas dosis
HER/EGFR	Receptor de factor de crecimiento epidérmico humano
HNA	Hormonoterapia neoadyuvante
HR	*Hazard ratio*
HT	Hormonoterapia
IA	Inhibidores aromatasa
IAE	Inhibidor no esteroideo de la aromatasa
IANE	Inhibidor de la no esteroideo de la aromatasa
IC	Intervalo de confianza
ICT	Células tumorales aisladas
IHQ	Inmunohistoquímico
ILE	Intervalo libre de enfermedad
IPM	Irradiación parcial de la mama
ISH	Hibridación *in situ*
L	Lapatinib
LA	Linfadenectomía axilar
LET	Letrozol
LHRH	Hormona liberadora de la hormona luteinizante
LR-SLP	Supervivencia libre de progresión locorregional
MMSE	*Mini-Mental State Examination*
MNA	*Mini nutritional assessment*
MRM	Mastectomía radical modificada
MT	Marcadores tumorales
N.A	No aportado
NAB-P	nab-paclitaxel (paclitaxel unido a albúmina)
NCCN	*National Comprehensive Cancer Network*
NCI	*National Cancer Institute*
NCI-CTCAE	*National Cancer Institute Common Terminology Criteria for Adverse Events*
N.S	No significativo
NSABP	*National Surgical Adjuvant Breast and Bowel Project*

OCCR	*Ovarian Cancer Cluster Region*
OR	*Odds Ratio*
ORR	*Objective response rate*
OSNA	*One step nucleic acid amplification*
P	Paclitaxel
PA	Palbociclib
PAAF	Punción aspiración con aguja fina
PE	Progresión de la enfermedad/pertuzumab
PEPI	*Preoperative Endocrine Prognostic Index*
PER	Pertuzumab
PET	Tomografía por emisión de positrones
PF	Preservación de la fertilidad
Post-Op	Postoperatorio
PP	Profilaxis primaria
pRC	Respuesta patológica completa
Pre-Op	Preoperatorio
pRP	Respuesta parcial patológica
pRPmic	Respuesta parcial patológica microscópica
PS	Profilaxis secundaria
QoL	Calidad de vida
QT	Quimioterapia
RANKL	Ligando del receptor activador del factor nuclear k-B
RC	Respuesta completa
RCB	*Residual Cancer Burden* (enfermedad residual posquimioterapia)
RE	Receptor de estrógeno
RFS	Supervivencia libre de recaída
RH	Receptor hormonal
RMN	Resonancia magnética nuclear
ROI	Rastreo óseo isotópico/ gamma o escintigrafía ósea
RP	Receptor de progesterona/Respuesta parcial
RR	Riesgo de recaída
RS	Recurrence score

RT	Radioterapia
Rx	Radiografía
SBRT	Radioterapia estereotáctica de cuerpo
SC	Subcutáneo
SERD	Inhibidor selectivo del RE
SERMS	Modulador selectivo del receptor estrogénico
SG	Supervivencia global
SLE	Supervivencia libre de enfermedad
SLP	Supervivencia libre de progresión
SLR	Supervivencia libre de recaída
SNP	*Single nucleotide polymorphism*
SPPB	Batería corta de rendimiento físico
ST	Tratamiento sistémico
T	Taxano
TA	Tratamiento adyuvante
TAC	Tomografía axial computarizada o Docetaxel, adriamicina, ciclofosfamida
TAM	Tamoxifeno
TBCRC	*Translational Breast Cancer Research Consortium*
TC	Docetaxel y ciclofosfamida
TCH	Docetaxel, carboplatino, trastuzumab
T-DM1	Trastuzumab emtansina
TE	Terapia endocrina
TIL	*Tumor Infiltrating Lymphocites*
THP	Tiempo hasta progresión
TMA	Transplante de células madre autólogo
TN	Triple negativo
TNA	Tratamiento neoadyuvante
TR	Trastuzumab
UCGC	Unidad de consejo genético en cáncer
UI	Unidades Internacionales
V	Vinorelbina

CAPÍTULO 8. TRATAMIENTO DE SOPORTE

A. HEMATOPOYÉTICO

¿Cuándo debemos administrar G-CSF?

¿Qué G-CSF es el más recomendado? ¿En qué momento debemos iniciar el tratamiento con G-CSF, con qué dosis y durante cuánto tiempo hay que mantenerlo?

¿Son seguros los factores estimuladores de la eritropoyesis (ESA) en el cáncer de mama?

VER RESUMEN
8. Tratamiento de soporte
a) Hematopoyético

En este apartado se resumen las indicaciones de profilaxis con G-CSF y su uso terapéutico en pacientes con cáncer de mama que reciben quimioterapia, así como las indicaciones de tratamiento con ESA en esas mismas pacientes.

USO DE FACTORES ESTIMULADORES DE COLONIAS GRANULOCÍTICAS (G-CSF) EN PACIENTES CON CÁNCER DE MAMA QUE RECIBEN QUIMIOTERAPIA

- La neutropenia inducida por la quimioterapia es la toxicidad limitante de dosis más común del tratamiento del cáncer.
- Los criterios más utilizados para establecer la gravedad de la neutropenia inducida por quimioterapia son los del NCI-CTCAE (*National Cancer Institute Common Terminology Criteria for Adverse Events*).
- El tratamiento con G-CSF en pacientes con cáncer de mama que reciben quimioterapia:
  - Reduce la incidencia, duración y severidad de la neutropenia inducida por la quimioterapia (561).
  - Permite la administración de dosis plenas de quimioterapia y la administración del número de ciclos planeados, así como el aumento de la intensidad o densidad de dosis (562).
  - Mejora la respuesta terapéutica y la supervivencia (563).
  - Reduce el coste de la neutropenia febril porque disminuye el número de hospitalizaciones y la necesidad de tratamiento con antibióticos intravenosos durante el tratamiento con quimioterapia (564, 565).

¿Cuándo debemos administrar G-CSF?

Los G-CSF pueden utilizarse como profilaxis (primaria o secundaria) o como tratamiento.

Profilaxis primaria

- La profilaxis primaria se define como el uso de G-CSF para prevenir la posibilidad de una fiebre neutropénica durante el primer ciclo de quimioterapia, cuando no ha ocurrido ningún episodio previo.
- La profilaxis primaria reduce el riesgo de fiebre neutropénica, permite aumentar la intensidad de la dosis de quimioterapia administrada y reduce el riesgo de muerte relacionada con la infección y el riesgo de muerte durante la quimioterapia (566-568).
- Para su utilización debemos valorar el riesgo que tiene la paciente de sufrir un episodio de fiebre neutropénica, para lo que tendremos en cuenta tanto el esquema de quimioterapia que vamos a utilizar (Tabla 89) como los factores de riesgo de cada paciente para tener una fiebre neutropénica (Tabla 90).

Tabla 90. Esquemas de quimioterapia utilizados en el cáncer de mama por riesgo de fiebre neutropénica (FN). ***Basada en Muñoz Langa J. et al. (569)***

Tumour type	FN risk category	CT regimen	FN risk (%)
Breast cancer	>20%	AC → docetaxel	5-25
		Docetaxel → AC	40
		Doxorubicin/docetaxel	33-48
		Doxorubicin/paclitaxel	21-32
		TAC	22-25 (no PP)
		DD/DDG FEC	71/59
		FEC-docetaxel	25-46
		DDG doxorubicin → paclitaxel → cyclophosphamide	2 (with PP)
		DDG doxorubicin/cyclophosphamide → paclitaxel	2 (with PP)
		DDG epurubicin/cyclophosphamide	8 (with PP)
	10-20%	Doxorubicin/vinorelbine	15
		Docetaxel	16-17
		Capecitabine/docetaxel	13
		Cyclophosphamine/mitoxantrone	11
		FEC-100	13-17 (with PP)
		AC	14
		Epidoxorubicin/cyclophosphamide	13
		CEF	14
		FEC 120	9-14
	<10%	CMF	0-3
		Oral CMF	1
		Doxorubicin/cyclophosphamide	0-3
		Doxorubicin → paclitaxel → cyclophosphamide	3
		Doxorubicin/cyclophosphamide → paclitaxel	5
		FAC 50	5
		Epirubicin/cyclophosphamide±lonidamine	7

Tabla 90. Factores de riesgo de fiebre neutropénica. ***Adaptada de Muñoz Langa J. et al. (569).***

Alto riesgo	Edad >65 años
Riesgo aumentado	Episodio previo de FN Enfermedad avanzada Sin uso previo de CSF o antibióticos
Otros factores de riesgo	Comorbilidades severas QT o RT previa Hemoglobina < 12 g/dl Infiltración de médula ósea Heridas abiertas o infecciones activas Mal estado general y nutricional Cirugía reciente Mujeres QT-RT concomitante

Indicaciones de profilaxis primaria:

- **Pacientes que reciben esquemas de quimioterapia con un riesgo de fiebre neutropénica > 20 %.**
- **Se puede considerar en pacientes que reciben esquemas de quimioterapia con un riesgo entre 10 y 20 %, en pacientes con factores de riesgo de fiebre neutropénica.**

En ambos casos se considerará el tratamiento si la intención de la quimioterapia es curativa o prolongar la supervivencia. Si la intención del tratamiento es el control de los síntomas, se administrará profilaxis primaria si se asocian otros factores de riesgo de fiebre neutropénica.

Profilaxis secundaria

La profilaxis secundaria se define como el uso de G-CSF para prevenir nuevos episodios de FN o neutropenias limitantes de dosis en pacientes que han sufrido un episodio de FN.

La profilaxis secundaria está indicada en:

- Pacientes con una neutropenia limitante de dosis en los casos en que la reducción o el retraso de dosis se asocie a un peor pronóstico.
- Pacientes que han presentado un episodio previo de fiebre neutropénica (siempre que no se administraran G-CSF previos).

Uso terapéutico

- Están indicados en pacientes que presenten factores de riesgo para tener complicaciones asociadas a la infección (569).
- Los factores de riesgo para desarrollar complicaciones asociadas a la infección son:
  - Edad > 65 años
  - Sepsis
  - Neutropenia severa (<100 neutrófilos) o prolongada (> 10 días)
  - Neumonía, infección fúngica invasiva u otras infecciones clínicamente documentadas
  - Pacientes hospitalizadas en el momento del episodio de fiebre
  - Episodios previos de fiebre neutropénica

¿Qué G-CSF es el más recomendado? ¿En qué momento debemos iniciar el tratamiento con G-CSF, con qué dosis y durante cuánto tiempo hay que mantenerlo?

- El filgrastim y el lenograstim son igual de eficaces en la prevención de la FN (566).
- El pegfilgrastim es más eficaz que el filgrastim en la prevención de la FN (570, 571).

Tabla 91. Factores estimuladores de colonias granulocíticas de uso en cáncer de mama: filgrastim.

Fármaco	Dosis	Presentación	Cuando iniciar	Duración del tratamiento
Filgrastim	5 µg/Kg/día SC.	Jeringas precargadas de 30 millones de UI (300 µg) o de 48 millones de UI (480 µg)	Entre 24 y 72 h después de la administración de la QT	Como PP: 5-7 días Como PS o tratamiento: hasta alcanzar cifras de neutrófilos >1500

PP: profilaxis primaria; PS: profilaxis secundaria, UI: unidades internacionales; QT: quimioterapia.

Tabla 92. Factores estimuladores de colonias granulocíticas de uso en cáncer de mama: lenograstim.

Fármaco	Dosis	Presentación	Cuando iniciar	Duración del tratamiento
Lenograstim	19,2 millones de UI/m^2 al día sc	Jeringas precargadas de 13,4 millones de UI (105 µg) o 34 millones de UI (263 µg)		

UI: unidades internacionales

Tabla 93. Factores estimuladores de colonias granulocíticas de uso en cáncer de mama: pegfilsgrastim.

Fármaco	Dosis	Presentación	Cuando iniciar	Duración del tratamiento
Pegfilgrastim	6mg sc	Bolígrafos precargados de 6 mg	24 horas después de la administración de la QT	1 sola administración cada 2 o cada 3 semanas

SC: subcutáneo; QT: quimioterapia.

USO DE FACTORES ESTIMULADORES DE LA ERITROPOYESIS

- La anemia (hemoglobina <12 mg/dl) es una complicación hematológica frecuente en las pacientes con cáncer. Su etiología es multifactorial pero produce un impacto importante en la calidad de vida de las pacientes.
- Los criterios más utilizados para establecer la gravedad de la anemia son los del NCI-CTCAE (493, 506, 507, 540, 541, 542, 549, 551, 554, 572).
- Los factores estimuladores de la eritropoyesis (ESAs) reducen la necesidad de transfusiones y los síntomas relacionados con la anemia (573).

Accede a las guías interactivas ESMO para el manejo de la anemia y déficit de hierro en pacientes con cáncer.

¿Son seguros los agentes estimuladores de la eritropoyesis (ESA) en el cáncer de mama?

- El tratamiento con ESA se ha asociado con un aumento de los accidentes tromboembólicos (574-578).
- El uso de ESA incrementa la mortalidad en pacientes que no reciben tratamiento para el cáncer o radioterapia (573).

Si se utilizan ESA, debe hacerse sólo en pacientes que reciben tratamiento, no se deben superar los 12gr/dl de hemoglobina y se debe sopesar muy bien el riesgo individual de cada paciente (577).

B. AGENTES MODULADORES DEL HUESO (AMH)

¿Existe un AMH de elección para la prevención de los eventos óseos relacionados con el esqueleto en la paciente con cáncer de mama y metástasis óseas?

¿Cuándo debemos iniciar el tratamiento con AMH en la paciente con metástasis óseas, con qué frecuencia y durante cuánto tiempo debemos mantenerlo?

¿Están indicados los AMH como tratamiento adyuvante?

¿Cuándo debemos administrar AMH para prevenir la pérdida de densidad mineral ósea (DMO)?

VER RESUMEN

8. Tratamiento de soporte

b) Agentes moduladores del hueso

Revisión del beneficio e indicaciones de tratamiento con AMH en pacientes con cáncer de mama.

Los agentes moduladores de hueso son un grupo de fármacos que actúan sobre la resorción ósea.

- Los bifosfonatos disminuyen la resorción ósea y aumentan la mineralización inhibiendo la actividad de los osteoclastos. Existen dos tipos de bifosfonatos: los no-nitrogenados y los nitrogenados. Los nitrogenados producen una inhibición más potente de la actividad osteoclástica.

- El denosumab es un anticuerpo monoclonal contra el ligando del receptor activador del factor nuclear k-B (RANKL). La inhibición de la resorción ósea se consigue porque el RANKL es un componente clave en la vía de formación y activación de osteoclastos.

- Los efectos secundarios comunes a todos los AMH son: hipocalcemia, fracturas atípicas y osteonecrosis mandibular. Los bifosfonatos intravenosos pueden producir reacciones de fase aguda con síntomas que incluyen dolor óseo, fiebre, fatiga, mialgias, artralgias y escalofríos, que habitualmente se resuelven en pocos días, así como toxicidad renal, mientras que los orales producen trastornos gastrointestinales. El denosumab se ha asociado con un mayor riesgo de infección y reacciones dermatológicas. La incidencia de osteonecrosis mandibular es baja (2-5 %), está relacionada con la dosis y la duración del tratamiento y su riesgo aumenta con la manipulación dental invasiva (579, 580).

Antes de iniciar cualquier tratamiento con AMH, todas las pacientes deben realizarse una revisión dental e iniciar la toma de calcio y vitamina D (1.000 mg de calcio y 800-1.000 mg UI de vitamina D).

- Los AMH se utilizan en el tratamiento del cáncer de mama en dos contextos:
    - En el cáncer de mama metástasico, para reducir los eventos relacionados con el esqueleto.
    - En el cáncer de mama precoz:
        - Para reducir la pérdida de DMO y de fracturas osteoporóticas que pueden ocasionar los tratamientos (quimioterapia, hormonoterapia).
        - Prevención de la metástasis

Tabla 94. Agentes moduladores de hueso disponibles para su uso en cáncer de mama. ***Creada por el autor.***

	Dosis	Frecuencia	Vía administración
Alendronato	70 mg(2)	semanal	oral
Ibandronato	50 mg(1)	diario	oral
	6 mg(1)	mensual	iv
	150 mg(2)	mensual	oral
Pamidronato	90 mg(1)	cada 3-4 semanas	iv
Risendronato	35 mg(2)	semanal	oral
Ácido zoledrónico	4 mg(1)	cada 3-4 semanas	iv
Clodronato	1600 mg(1)	diario	oral
Denosumab	120 mg (1)	mensual	sc
	60 mg(2)	cada 6 meses	sc

(1)Prevención de eventos relacionados con el esqueleto,
(2) Prevención de la pérdida de densidad mineral ósea; iv: intravenoso; sc: subcutáneo

USO DE AMH EN PACIENTES CON METÁSTASIS ÓSEAS PARA PREVENIR EVENTOS RELACIONADOS CON EL ESQUELETO

- La incidencia de metástasis óseas en el cáncer de mama se estima en un 65-75 % (581).
- Las complicaciones de las metástasis óseas se agrupan bajo el término de eventos relacionados con el esqueleto (ERE) e incluyen fracturas, compresiones medulares, necesidad de cirugía o radioterapia e hipercalcemia tumoral. Los ERE afectan negativamente a la calidad de vida de las pacientes y se asocian a elevados costes de tratamiento (582).
- Antes del uso de los AMH, las pacientes con CMM tenían un riesgo superior al 60 % a los dos años de desarrollar un evento óseo.
- Los AMH reducen de forma significativa los ERE en pacientes con cáncer de mama y metástasis óseas, y retrasan la aparición de dichos eventos. La introducción del pamidronato reducía el riesgo en un 33 % cuando se comparaba con el placebo (583). El ácido zoledrónico añade un 20 % de reducción de riesgo sobre la que ya producía el pamidronato (584). El denosumab reduce en un 22 % el riesgo de ERE comparado con los bifosfonatos (585).

¿Existe un AMH de elección para la prevención de los eventos óseos relacionados con el esqueleto en la paciente con cáncer de mama y metástasis óseas?

- El ácido zoledrónico es el bifosfonato más efectivo en la prevención de eventos óseos (584, 586).
- El denosumab es más efectivo que el ácido zoledrónico para prevenir eventos óseos (585).

El denosumab, por su eficacia, vía de administración y perfil de efectos secundarios, debería ser de elección; sin embargo, el ácido zoledrónico puede considerarse una opción alternativa a denosumab, salvo en las pacientes con aclaramientos de creatinina por debajo de 30 mil/min o en diálisis que deben ser tratadas siempre con denosumab.

¿Cuándo debemos iniciar el tratamiento con AMH en la paciente con metástasis óseas, con qué frecuencia y durante cuánto tiempo debemos mantenerlo?

Los AMH deben administrase lo antes posible en las pacientes con cáncer de mama con evidencia de destrucción ósea, independientemente de los síntomas que presenten.

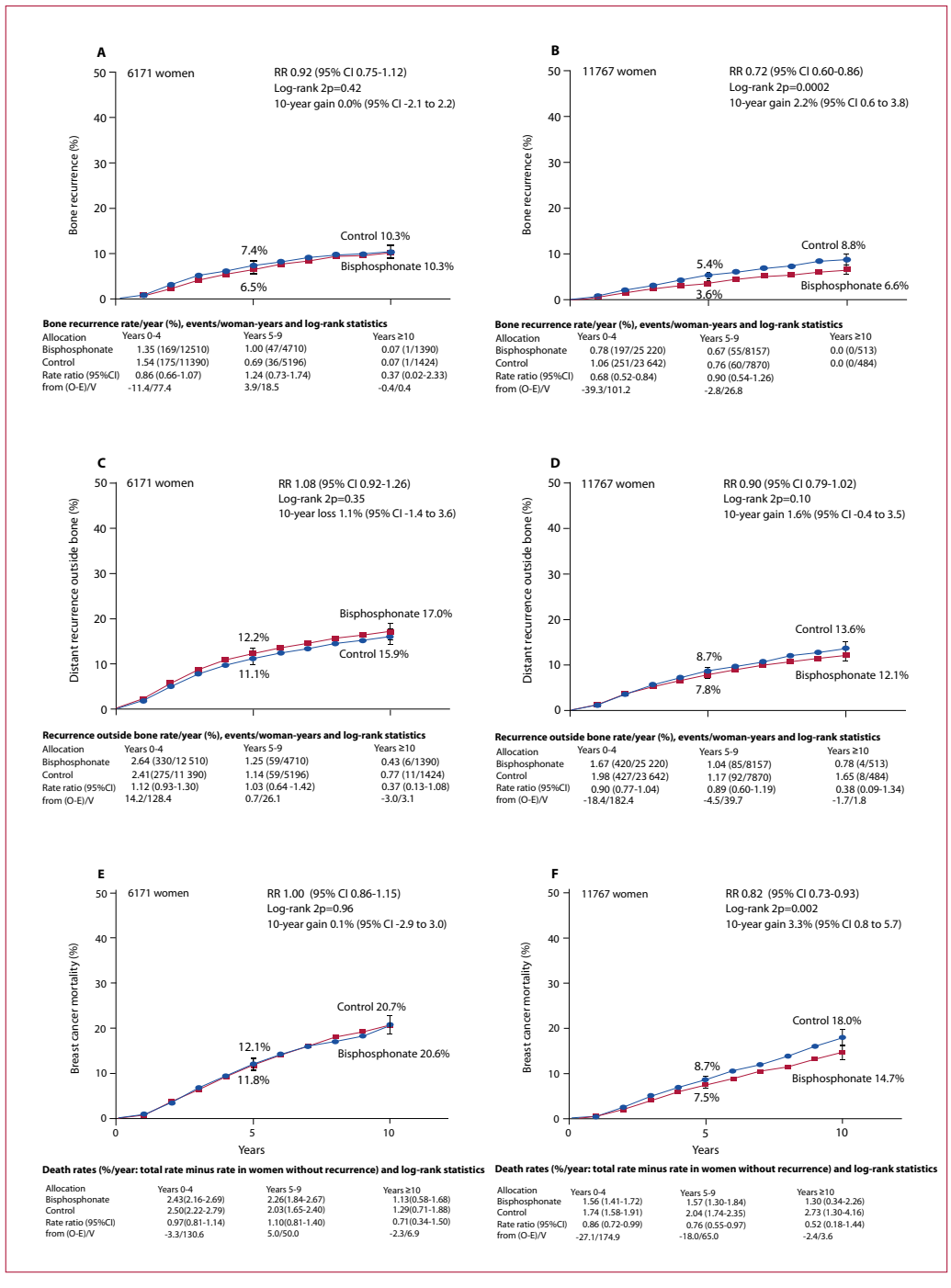
- Según la Guía de salud ósea en pacientes con cáncer de la ESMO, la destrucción ósea debe constatarse con una RX simple, una TAC o una RMN. La existencia de un rastreo óseo anormal, sin evidencia de destrucción ósea con una radiología simple, TAC o RNM, no justifica el inicio de tratamiento con AMH (587).
- El tratamiento con AMH no está indicado en pacientes sin evidencia de metástasis óseas, aunque tengan otras localizaciones metastásicas.
- La frecuencia aprobada de administración del ácido zoledrónico es cada cuatro semanas; sin embargo, existen ya datos de tres estudios aleatorizados (588-590) que demuestran que la administración del ácido zoledrónico cada 12 semanas es igual de efectiva en la prevención de eventos óseos. Se recomienda el tratamiento mensual con ácido zoledrónico durante 3-6 meses antes de iniciar la administración cada 12 semanas.
- El denosumab debe administrarse cada cuatro semanas; estudios en los pacientes con osteoporosis han mostrado una osteolísis de rebote, asociado con un aumento de fracturas vertebrales por lo que no deben recomenadarse las pautas de adminsitración menos frecuentes.
- Además si se suspende el tratamiento con denosumab durante más de 6 meses se debe administrar un bisfosfonato para mitigar este efecto.
- En ausencia de evidencia científica se recomienda continuar el tratamiento con AMH indefinidamente, si no existe excesiva toxicidad y mientras se mantenga el beneficio.

USO DE AMH COMO TRATAMIENTO ADYUVANTE

¿Están indicados los AMH como tratamiento adyuvante?

- Los bifosfonatos reducen el riesgo de recaída y muerte en pacientes con cáncer de mama precoz con bajos niveles de estrógenos (premenopáusicas con supresión ovárica y posmenopáusicas) (591-593).

Figura 39. Efecto de los bifosfonatos en el riesgo de recaída y la mortalidad por cáncer de mama. ***Basada en Rosen L.S. et al. (584).***



Bone recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0-4	Years 5-9	Years ≥10
Bisphosphonate	1.35 (169/12510)	1.00 (47/4710)	0.07 (1/1390)
Control	1.54 (175/11390)	0.69 (36/5196)	0.07 (1/1424)
Rate ratio (95%CI)	0.86 (0.66-1.07)	1.24 (0.73-1.74)	0.37 (0.02-2.33)
from (O-E)/V	-11.4/77.4	3.9/18.5	-0.4/0.4

Bone recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0-4	Years 5-9	Years ≥10
Bisphosphonate	0.78 (197/25 220)	0.67 (55/8157)	0.0 (0/513)
Control	1.06 (251/23 642)	0.76 (60/7870)	0.0 (0/484)
Rate ratio (95%CI)	0.68 (0.52-0.84)	0.90 (0.54-1.26)	
from (O-E)/V	-39.3/101.2	-2.8/26.8	

Recurrence outside bone rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0-4	Years 5-9	Years ≥10
Bisphosphonate	2.64 (330/12 510)	1.25 (59/4710)	0.43 (6/1390)
Control	2.41(275/11 390)	1.14 (59/5196)	0.77 (11/1424)
Rate ratio (95%CI)	1.12 (0.93-1.30)	1.03 (0.64 -1.42)	0.37 (0.13-1.08)
from (O-E)/V	14.2/128.4	0.7/26.1	-3.0/3.1

Recurrence outside bone rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0-4	Years 5-9	Years ≥10
Bisphosphonate	1.67 (420/25 220)	1.04 (85/8157)	0.78 (4/513)
Control	1.98 (427/23 642)	1.17 (92/7870)	1.65 (8/484)
Rate ratio (95%CI)	0.90 (0.77-1.04)	0.89 (0.60-1.19)	0.38 (0.09-1.34)
from (O-E)/V	-18.4/182.4	-4.5/39.7	-1.7/1.8

Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0-4	Years 5-9	Years ≥10
Bisphosphonate	2.43(2.16-2.69)	2.26(1.84-2.67)	1.13(0.58-1.68)
Control	2.50(2.22-2.79)	2.03(1.65-2.40)	1.29(0.71-1.88)
Rate ratio (95%CI)	0.97(0.81-1.14)	1.10(0.81-1.40)	0.71(0.34-1.50)
from (O-E)/V	-3.3/130.6	5.0/50.0	-2.3/6.9

Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0-4	Years 5-9	Years ≥10
Bisphosphonate	1.56 (1.41-1.72)	1.57 (1.30-1.84)	1.30 (0.34-2.26)
Control	1.74 (1.58-1.91)	2.04 (1.74-2.35)	2.73 (1.30-4.16)
Rate ratio (95%CI)	0.86 (0.72-0.99)	0.76 (0.55-0.97)	0.52 (0.18-1.44)
from (O-E)/V	-27.1/174.9	-18.0/65.0	-2.4/3.6

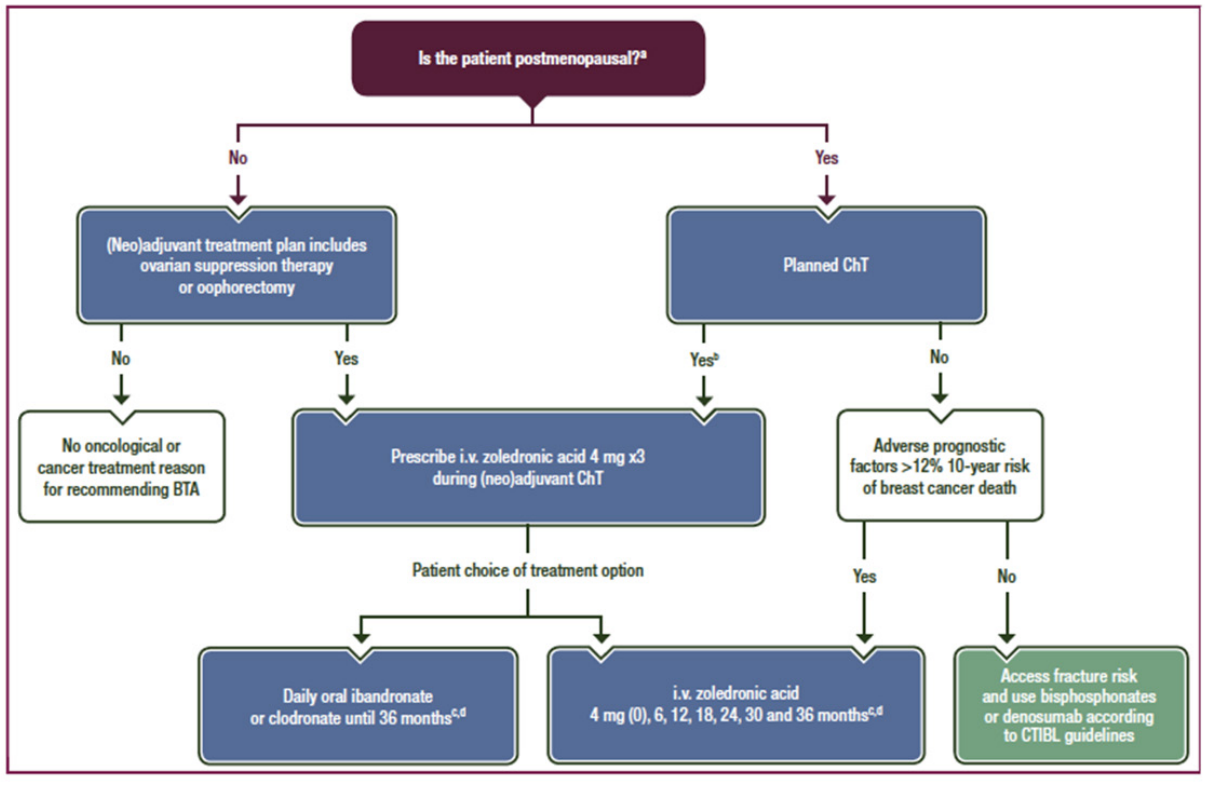
Figure 3: Main outcomes in premenopausal (excluding perimenopausal) and in postmenopausal women in trials of bisphosphonate versus no bisphosphonate (control)
Kaplan-Meier graphs showing the effects of treatment allocation on 10-year breast cancer outcomes. (A) Premenopausal and (B) postmenopausal bone recurrence.(C) Premenopausal and (D) postmenopausal distant recurrence outside the bone. (E) Premenopausal and (F) postmenopausal breast cancer mortality. O-E= observed minus expected. V= variance of O-E. RR= rate ratio (exp[(O-E)/V]). Error bars are SE.

- En el estudio ABCSG-18 el denosumab aumenta la supervivencia libre de enfermedad (HR 0,82; IC 95 % 0,69–0,98) (594) en pacientes posmenopáusicas que reciben tratamiento con inhibidores de aromatasa, aunque los beneficios aparentes del denosumab se deben a la reducción de segundos cánceres (no de mama) y muertes sin recaídas más que a la prevención de las recaídas de cáncer de mama. En el estudio D-CARE, sin embargo, no se encuentran diferencias en la supervivencia libre de metástasis óseas con el tratamiento adyuvante con denosumab (HR 0,97; IC 95% 0,82 1,14) pacientes con estadios II y III de cáncer de mama que reciben tratamiento adyuvante o neoadyuvante (595).

¿Cuándo debemos administrar AMH para prevenir la pérdida de densidad mineral ósea (DMO)?

- Los tratamientos adyuvantes administrados a las pacientes con cáncer de mama aumentan el riesgo de osteoporosis. La osteoporosis se asocia con un riesgo aumentado de fracturas (596) y puede asociarse con una mayor morbimortalidad.
- Los bifosfonatos y el denosumab previenen la pérdida de densidad mineral ósea asociada con la supresión ovárica o el tratamiento con inhibidores de aromatasa (597, 598).
- En las pacientes que hayan recibido tratamientos que pueden disminuir la densidad mineral ósea, debe realizarse una historia clínica detallada recogiendo antecedentes familiares de osteoporosis u otros factores de riesgo y una densitometría basal antes de iniciar el tratamiento.

Figura 40. Algoritmo diagnóstico y terapéutico de la pérdida de densidad mineral ósea asociada a los tratamientos del cáncer de mama. ***Basada en Hadji P. et al. (587)*****.**



C. CUIDADOS PALIATIVOS

En el cáncer de mama metastásico, ¿cuándo debemos interrumpir el tratamiento activo?

En el cáncer de mama metastásico, ¿cuándo debemos interrumpir el tratamiento activo?

- El objetivo del tratamiento del cáncer de mama metastásico es aumentar la supervivencia y mejorar la calidad de vida de las pacientes mediante el control de los síntomas.
- No existe evidencia científica que apoye cuándo es el momento de finalizar el tratamiento activo; sin embargo parece razonable interrumpirlo cuando el tratamiento no consigue controlar los síntomas o la toxicidad del mismo empeora la calidad de vida de la paciente (375).
- La decisión de parar el tratamiento debe atender a estas razones, pero también a las preferencias de las pacientes. Esta decisión debe tomarse de común acuerdo con ella y tras una información adecuada sobre el beneficio del tratamiento en cada momento (si aumenta la supervivencia y cuánto tiempo, si solo consigue controlar síntomas, si puede conseguir ambas cosas) y cuando no es posible conseguir ninguno de estos objetivos con los tratamientos disponibles.

D. MANEJO DE TOXICIDADES

¿Qué fármacos utilizados en el tratamiento del cáncer de mama pueden producir toxicidad cardiovascular?

¿Existen diferentes tipos de cardiotoxicidad? ¿Puede prevenirse la toxicidad cardíaca derivada de los tratamientos?

¿Cuáles son los factores de riesgo para desarrollar una neuropatía por paclitaxel?

¿Hay algún tratamiento para prevenir la neuropatía por paclitaxel? La neuropatía por paclitaxel ¿tiene tratamiento?

¿Qué hacer ante una extravasación?

Revisión de las toxicidades que por importancia o frecuencia afectan más a las pacientes con cáncer de mama que reciben tratamiento con quimioterapia: cuáles son los fármacos que las producen, el mecanismo de acción, el tratamiento ante su aparición y la prevención de los mismos.

VER RESUMEN
8. Tratamiento de soporte
d) Manejo de toxicidades

TOXICIDAD CARDÍACA

Los largos supervivientes de un cáncer que han sido tratados con tratamientos cardiotóxicos o radioterapia deben ser informados del riesgo aumentado de enfermedades cardiovasculares. El screening cardiovascular reduce la incidencia de fallo cardíaco en un 18%, aunque no existe consenso acerca del screening óptimo y la frecuencia del mismo.

En la Guía de toxicidad cardiovascular en pacientes con cáncer de la ESMO, se detallan los fármacos que pueden producir toxicidad, cuáles son los factores de riesgo y cómo debe realizarse una adecuada monitorización de dicha toxicidad (599)

¿Qué fármacos utilizados en el tratamiento del cáncer de mama pueden producir toxicidad cardiovascular?

Tabla 95. Cardiotoxicidad de los tratamientos utilizados en el cáncer de mama. ***Basada en Zagar T.M. et al. (600).***

Clase	Fármaco	Efectos tóxicos
Agentes citostáticos		
Antraciclinas/análogos	Doxorrubicina, daunorrubicina y epirrubicina	Disminución progresiva de la función del ventrículo izquierdo conduciendo a una insuficiencia cardíaca manifiesta, arritmias auriculares y/o ventriculares, pericarditis/miocarditis
Agentes alquilantes	Ciclofosfamida, cisplatino	Pericarditis/miocarditis, disfunción ventricular izquierda aguda, arritmias auriculares/ventriculares y trombosis, isquemia y/o infarto miocárdico, disfunción del ventrículo izquierdo, arritmias, daño endovascular
Agentes antimicrotubulares	Paclitaxel, docetaxel	Bradicardia, bloqueo auriculoventricular, arritmias auriculares y/o ventriculares
Análogos de pirimidinas	5-fluorouracilo, capecitabina	Espasmo y/o isquemia coronaria
Terapias dirigidas		
Anti-HER2	Trastuzumab, lapatinib	Disminución progresiva de la función del ventrículo izquierdo conduciendo a una insuficiencia cardíaca manifiesta
Inhibidores de la angiogénesis/ anti-VEGF	Bevacizumab	Hipertensión, infarto de miocardio, disfunción del ventrículo izquierdo, trombosis venosa, ictus y daño endovascular
Inhibidores de ciclinas	Ribociclib	Alarga el intervalo QT
Terapia endocrina		
Inhibidores de la aromatasa	Tamoxifeno, anastrazol, letrozol, exemestano	Eventos trombóticos, hipertensión, hipercolesterolemia

¿Puede prevenirse la toxicidad cardíaca derivada de los tratamientos?

Las medidas para prevenir la cardiotoxicidad en pacientes con cáncer de mama son:

- Independientemente de si reciben tratamientos cardiotóxicos o no:
  - Realizar ejercicio físico de forma regular
  - Identificar y controlar los factores de riesgo cardiovascular antes, durante y después del tratamiento (**Tabla 96**)

Tabla 96. Factores de riesgo de disfunción ventricular, en pacientes tratados con fármacos antitumorales y radioterapia (si el volumen de irradiación incluye, total o parcialmente, el corazón) (601).

Factores de riesgo de DV-CTOX	Antraciclinas	Anti-HER2	Anti-VEGF	Radioterapia torácica
Factores genéticos	X			
Dosis acumulada	X			≥35 Gy o ≥2 Gy / día
Mujeres	X			X
<15 o > 65 años	X	X		X
Hipertensión arterial	X	X	X	
Cardiopatía isquémica	X	X	X	X
FEVI en rango bajo de la normalidad (50-55%) antes del tratamiento [11,12]	X	X		
Historia de insuficiencia cardíaca/DV-CTOX	X	X	X	
Tratamiento combinado antitumorales* y radioterapia torácica	X	X	X	X
Insuficiencia renal	X			
Obesidad (IMC>30) y sedentarismo		X		
Tiempo transcurrido desde el tratamiento				X

anti-HER2: fármacos que bloquean el receptor 2 del factor de crecimiento epidérmico humano; anti-VEGF: fármacos inhibidores del facotr de crecimiento del endotelio vascular; DV-CTOX: disfunción ventricular secundaria a cardiotóxicos; FEVI: fracción de eyección del ventrículo izquierdo; IMC: índice de masa corporal;

**Fármacos de riesgo alto: antraciclinas, ciclofosfamida, trastuzumab; de riesgo moderado: docetaxel, pertuzumab, sunitinib, sorafenib; de riesgo bajo: bevacizumab, dasatanib, imatinib y lapatinib.*

- Durante la administración de tratamientos potencialmente cardiotóxicos:
  - Utilización de esquemas terapéuticos menos cardiotóxicos si es posible (formulaciones liposomiales).
  - Los bloqueadores beta (carvedilol y nebivolol) previenen la reducción de la FEVI y disminuyen la incidencia de la insuficiencia cardíaca durante el tratamiento con trastuzumab y/o antraciclinas (602, 603). El enalapril previene el deterioro de la FEVI en pacientes con elevación de troponinas durante el tratamiento con antraciclinas (604). El candesartán ha demostrado un efecto cardioprotector frente al placebo (ensayo PRADA) (605).
  - Las pacientes con hiperlipidemia se benefician del tratamiento hipolipemiante durante el tratamiento activo

Figura 41. Algoritmo de seguimiento para prevención de la toxicidad cardíaca secundaria a tratamientos cardiotóxicos (601).

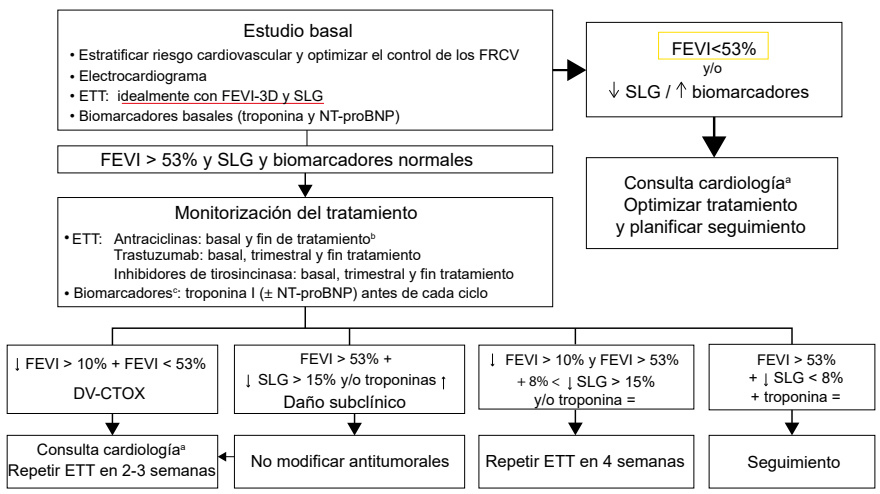


Figura 2. Algoritmo de monitorización del tratamiento con fármacos antitumorales[14]. 3D: tridimensional; DV-CTOX: disfunción ventricular secundaria a cardiotóxicos; ETT: ecocardiograma transtorácico; FEVI: fracción de eyección del ventrículo izquierdo; FRCV: factores de riesgo cardiovascular; NT-proBNP: fracción aminoterminal del propéptido natriurético cerebral; SLG: *strain* longitudinal global. [a]Idealmente, consulta específica de cardio-onco-hematología. [b]Se recomienda revaluar la FEVI antes de finalizar el tratamiento si se supera una dosis acumulada de 240 mg/m^2. En estos casos, debe monitorizarse la FEVI periódicamente hasta el final del tratamiento. [c]En pacientes de bajo riesgo cardiovascular y sin antecedentes de tratamientos cardiotóxicos, la determinación de troponinas antes de cada ciclo reduce el número de ecocardiogramas y los limita a pacientes con síntomas o elevación de troponinas.

Toxicidad cardíaca secundaria a antraciclinas

- La toxicidad cardíaca por antraciclinas puede ser de presentación aguda, subaguda o tardía. La toxicidad aguda es poco frecuente, ocurre durante la infusión del fármaco o durante las horas posteriores, cursa con cambios electrocardiográficos inespecíficos y normalmente se resuelve al finalizar la infusión. La forma subaguda también es poco frecuente, ocurre de días a semanas después del tratamiento y se han descrito algunos casos de pericarditis-miocarditis e insuficiencia cardíaca aguda. La toxicidad tardía aparece durante el periodo variable entre un año y 10 a 30 años después del uso de los fármacos.

- La miocardiopatía producida por antraciclinas puede ser inicialmente asintomática o subclínica para después evolucionar a un deterioro de la función ventricular con disfunción diastólica o disfunción sistólica. Dado que el diagnóstico precoz puede ayudar a minimizar los efectos cardíacos de las antraciclinas, se recomienda una adecuada monitorización de estas pacientes. Además, pueden aparecer arritmias asociadas.
- Los factores de riesgo relacionados con la toxicidad por antraciclinas se señalan en la **Tabla 96**.
- Aunque la evidencia histórica muestra que la toxicidad cardíaca secundaria a las antraciclinas es irreversible, la evidencia actual demuestra que el diagnóstico precoz de la cardiotoxicidad inducida por antraciclinas y su tratamiento puede mejorar la fracción de eyección cardíaca e incluso elevarla hasta límites normales.
- Es de gran importancia detectar la disfunción cardíaca cuando es subclínica para instaurar un tratamiento de forma precoz, porque si la disfunción cardíaca subclínica no se trata antes de seis meses, las posibilidades de recuperación son muy bajas (606, 607).
- Dado que el diagnóstico precoz puede ayudar a minimizar los efectos cardíacos de las antraciclinas, se recomienda una adecuada monitorización de estas pacientes (601, 608), que consiste en:
  - Determinación de troponina, pro-BNP antes de cada ciclo (599).
  - Reevaluación de la FEVI cuando la dosis de doxorrubicina sea de 250 mg / m2 o su equivalente antraciclina, después de aproximadamente cada 100 mg / m2 adicionales (o aproximadamente epirrubicina 200 mg / m2) más allá de 250 mg / m2 y al final de la terapia, incluso si <400 mg / m2 (599).

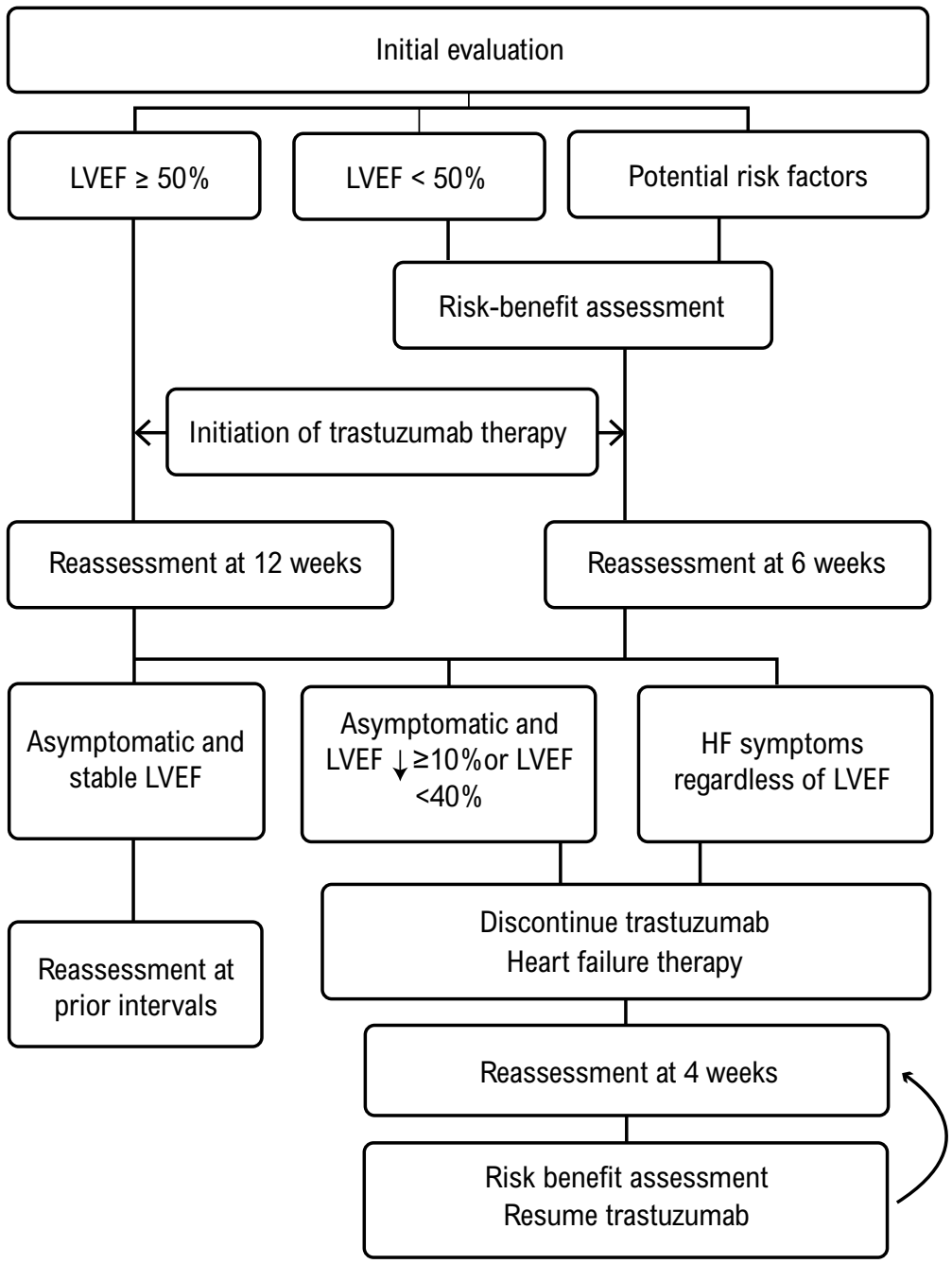
Toxicidad cardíaca por tratamiento anti-HER2

Trastuzumab

- La incidencia de toxicidad cardíaca inducida por trastuzumab varía dependiendo de la definición de la misma utilizada en los diferentes estudios. Los datos de un metaanálisis donde se analizan los cinco estudios de tratamiento adyuvante indican que el riesgo de cardiotoxicidad es 2,5 veces superior (609).
- La incidencia de cardiotoxicidad aumenta cuando se administran concomitantemente con antraciclinas y en tratamientos más largos (610, 611).
- La combinación con otros fármacos, como los taxanos, no incrementa significativamente los episodios de insuficiencia cardíaca congestiva.
- La administración concomitante de trastuzumab y/o pertuzumab con antraciclinas liposomiales se ha demostrado segura (612, 613).
- La cardiotoxicidad producida por el trastuzumab suele ser asintomática, con un descenso en la fracción de eyección del ventrículo izquierdo, y es menos frecuente que produzca insuficiencia cardíaca congestiva.

- Los factores de riesgo para la cardiotoxicidad por trastuzumab son: el uso concomitante con antraciclinas, la hipertensión, la edad > 50 años, una disfunción cardíaca previa y un índice de masa corporal superior a 25.
- **La combinación de trastuzumab con antraciclinas convencionales no se recomienda, por el alto riesgo de insuficiencia cardíaca congestiva, que puede llegar hasta el 16 %** (208).
- Debe realizarse una adecuada valoración previa al tratamiento y durante el mismo con ecocardiografía cada 12 semanas y biomarcadores (troponina y proBNP) (figura 42).

Figura 42. Monitorización recomendada durante el tratamiento con trastuzumab (614).



LVEF: Fracción de eyección del ventrículo izquierdo (FEVI)

Pertuzumab

- **La combinación de pertuzumab con trastuzumab no aumenta el riesgo de cardiotoxicidad** (432).

TDM-1

- Los datos del estudio EMILIA, que compara TDM-1 con lapatinib capecitabina en CM metastásico HER2 positivo tratados previamente con trastuzumab, muestran que solo un 1,7 % de las pacientes en el grupo de T-DM1 tuvieron una reducción de la FEVI, y que esta fue de grado 3 solo en el 0,2 % de las pacientes (615).

Tratamiento de la miocardiopatía

El tratamiento utilizado es el de la insuficiencia cardíaca por miocardiopatía de otras causas, ya que no existen guías concretas para el tratamiento de la disfunción cardíaca producida por fármacos antineoplásicos. En pacientes con FEVI deprimida, asintomática o sintomática, debe tratarse con beta-bloqueadores e IECA para evitar la IC clínica (601).

TOXICIDAD NEUROLÓGICA DEL PACLITAXEL

La toxicidad neurológica más frecuente del paclitaxel es una neuropatía sensitiva limitante de dosis que afecta predominantemente a la sensibilidad térmica y dolorosa, además de la vibratoria y posicional (60 %), aunque puede causar también una neuropatía motora.

- La manifestación más frecuente de la neuropatía sensitiva son las parestesias en manos y pies y la pérdida de reflejos. A medida que aumenta su severidad, produce ataxia y torpeza de manos que interfiere con las actividades de la vida diaria.
- La neuropatía motora afecta a los músculos proximales.
- Tras completar el tratamiento, 1/3 de las pacientes mejoran en un período de cuatro a seis meses; sin embargo, en otras puede persistir.
- Hasta en el 80 % de las pacientes tiene síntomas más allá de los dos años de completar el tratamiento.
    - La escala de valoración de toxicidad neurológica más utilizada es la del NCI-CTCAE y, específicamente, la subescala de toxicidad neurológica sensitiva.

¿Cuáles son los factores de riesgo para desarrollar una neuropatía por paclitaxel?

- Neuropatía previa.
- Dosis acumulada (1000 mg/m^2) (616).
- Esquema de administración. Aunque los estudios que comparan paclitaxel **semanal con cada tres semanas describen una mayor toxicidad con la administración** semanal (617, 618), los datos de un metaanálisis de siete ensayos aleatorizados que comparan la administración semanal de docetaxel y paclitaxel con la trisemanal no encuentran diferencias en la incidencia de neuropatía (619).
- El efecto de la duración de la infusión en la incidencia de neuropatía tampoco está claro; hay estudios que muestran mayor incidencia de toxicidad neurológica con las infusiones largas en cáncer de mama (620), y sin embargo otros, en cáncer de ovario, no encuentran diferencias al comparar las infusiones de tres horas con las de 24.
- Síndrome de dolor agudo asociado a paclitaxel. Es una forma aguda de neuropatía que se manifiesta con artralgias, mialgias, entumecimiento y hormigueo. Comienza dos o tres días después del tratamiento y suele durar de cuatro a cinco días. Su aparición se relaciona con la neuropatía inducida por paclitaxel (621).
- Variabilidad interindividual, *Single Nucleotide Polymorphism* (SNPs).
- No se ha demostrado que la diabetes y la neuropatía periférica idiopática sean factores de riesgo para desarrollar una neuropatía por paclitaxel.

¿Hay algún tratamiento para prevenir la neuropatía por paclitaxel? La neuropatía por paclitaxel ¿tiene tratamiento?

- Sobre la base de la evidencia, no hay ningún tratamiento que prevenga esta neuropatía (622).
- Para el tratamiento de la misma puede utilizarse la duloxetina (623).

LINFEDEMA (558, 559)

- La incidencia de linfedema en supervivientes de cáncer de mama varía entre un 5 y un 40 %.
- La incidencia más alta se produce en las pacientes en las que se practicó un vaciamiento axilar y que recibieron radioterapia. En las pacientes en las que solo se hizo biopsia de ganglio centinela, la incidencia de linfedema es de un 5 % (624, 625).
- Es fundamental informar adecuadamente a las pacientes que han sido sometidas a una linfadenectomía axilar y/o radioterapia sobre las medidas para prevenir el linfedema (**Tabla 97**).
- El inicio suele ser insidioso y progresivo aunque, en algunos casos, el debut puede ser brusco, en relación con una infección, un traumatismo o la picadura de un insecto.

- El diagnóstico es fundamentalmente clínico.
- Cuando se detecte un linfedema tras varios años desde la cirugía, sin un trauma previo, habrá que descartar como primera causa una recaída locorregional.
- La principal complicación del linfedema son las infecciones cutáneas.
- El tratamiento del linfedema consiste en la terapia física descongestiva (drenaje linfático, cinesiterapia, vendajes compresivos). La cirugía se reserva para casos muy seleccionados.
- Los diuréticos no son útiles en el tratamiento del linfedema (626, 627).

Tabla 97. Medidas para la prevención del linfedema. ***Adaptada de Droz J. et al. (627).***

1. Evitar inyecciones, administraciones intravenosas
2. Evitar heridas, quemaduras o picaduras
3. Evitar las mangas y accesorios ajustados

TOXICIDAD COGNITIVA

- Entre un 16 y un 75 % de las pacientes que reciben quimioterapia refieren algún tipo de déficit cognitivo durante la misma (628).
- Los déficits cognitivos en pacientes con CM tratadas previamente con quimioterapia son de poca magnitud al cabo de seis meses de la finalización del tratamiento, y se centran en habilidades verbales y visoespaciales (629).

EXTRAVASACIONES Y TOXICIDADES POR FÁRMACO

Extravasación y efectos adversos (Apartado *Policies&Procedures* en: http://www.bccancer.bc.ca/health-professionals/clinical-resources/systemic-therapy)

Tabla 98. Clasificación de los citostáticos más utilizados en el tratamiento del cáncer de mama según su capacidad de daño tisular tras su extravasación. *Basada en Conde-Estévez D. et al. (630).*

Vesicantes	Irritantes	No agresivos
Doxorrubicina	Irritantes de alto riesgo	Anticuerpos monoclonales
Epirrubicina	Docetaxel	Carboplatino[2]
Mitoxantrona	Doxorrubicina liposomal pegilada	Metotrexato
Paclitaxel	Irritantes de bajo riesgo	
Vinorelbina	Ciclofosfamida[1]	
	Doxorrubicina liposomal no pegilada	
	Fluorouracilo	
	Gemcitabina	

[1]En gran cantidad podría ser vesicante/irritante
[2]Según su mecanismo de acción o características fisioquímicas o estudios animales, sin casos ni estudios descritos en seres humanos.

¿Qué hacer ante una extravasación?

En el caso de sospechar una extravasación, se adoptará inmediatamente una serie de **medidas iniciales generales** y, después, se aplicará un tratamiento específico, si lo hubiera.

- En primera instancia, se deberá parar la infusión
- Aspirar a través de la aguja de infusión el posible fármaco residual del espacio extravascular
- Retirar la aguja
- Mantener la extremidad elevada

Las **medidas específicas** pueden comprender medidas físicas, como la aplicación local de frío o calor seco, y/o tratamiento farmacológico, como el uso de antídotos, según el caso. En caso de fracaso de estas medidas, se deberá valorar la intervención quirúrgica reparadora.

Tabla 99. Medidas específicas en la extravasación de los citostáticos utilizados en el tratamiento del cáncer de mama. ***Basada en Conde-Estévez D. et al. (630).***

Tabla 2 Resumen de medidas específicas en la extravasación de citostáticos según la evidencia actual

Citostáticos	Condiciones	Medidas farmacológicas	Medidas físicas	Medidas adicionales
Derivados del Pt				
Cisplatino[10]	>0,4 mg/ml	DMSO 90-99% tópico, 4 gotas/ 10 cm^2 de superfície cutánea cada 8 h en el doble del área afectada durante 7-14 días. Dejar secar al aire sin vendajes	Frío local durante 1 hora repetido cada 8 h, tras la aplicación de DMSO, durante 3 días.	
Antraciclinas				
Doxorubicina Daunorubicina **Epirubicina** Idarubicina[10,22,33]	- Extravasación confirmada de volumen > 5 mL o - Sospecha de extravasación de volumen > 10 mL o - Extravasación a través de vía central	Dexrazoxano[b] IV en perfusión de 1-2 h una vez al día durante 3 días en el brazo contralateral. Dosis diarias: 1.000, 1.000 y 500 mg/m^2. 1ª dosis antes de 6 h post-extravasación, luego a las 24 y 48 h.	-	Si aparición de lesión: uso de GM-CSF 1 ml de GM-CSF (300 mg/l) diluido en 9 ml de suero fisiológico (solución de 30 mg/l). Administrar varias inyecciones en bordes de úlcera[36]
	Ninguna de las anteriores	DMSO 90-99% tópico, 4 gotas/ 10 cm^2 de superfície cutánea cada 8 h en el doble del área afectada durante 7-14 días. Dejar secar al aire sin vendajes[10]	Frío local durante 1h repetido cada 8 h tras la aplicación de DMSO, durante 3 días[10]	
Antraciclinas liposomales				
Doxorubicina liposomal	-	DMSO 90-99% tópico, 4 gotas/ 10 cm^2 de superfície cutánea cada 8 h en el doble del área afectada durante 7-14 días. Dejar secar al aire sin vendajes	Frío local durante 1h repetido cada 8 h tras la aplicación de DMSO, durante 3 días	-
Alcaloides de la vinca				
Vinorelbina	-	Hilauronidasa 250 U en 6 ml de suero fisiológico administradas en 6 punciones subcutánas alrededor de la zona afectada	Calor moderado seco local durante 30 min tras la hialuronidasa. Alternativamente 15 minutos cada 6 horas por 2 días	-
Taxanos				
Paclitaxel **Docetaxel**[49]	-	Hilauronidasa 250 U en 6 ml de suero fisiológico administradas en 6 punciones subcutáneas alrededor de la zona afectada	Ninguna	-

GM-CSF: factor estimulante de colonias de granulocitos-macrófagos
[a] Estudio de animales sin casos descritos en seres humanos
[b] Savene® 20 mg/ml

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E. FERTILIDAD

¿Cómo estimar la reserva ovárica en las pacientes con cáncer de mama?

¿Qué factores influyen en la pérdida de la fertilidad y en la posibilidad de recuperación de la misma?

¿De qué técnicas disponemos para preservar la fertilidad en las pacientes con cáncer de mama?

¿El embarazo tras el tratamiento de un cáncer de mama es seguro?

VER RESUMEN
8. Tratamiento de soporte
e) Fertilidad

Análisis del efecto de los tratamientos del cáncer de mama sobre la fertilidad y revisión de las técnicas disponibles para preservar la fertilidad en pacientes con cáncer de mama.

La pérdida de la fertilidad es uno de los efectos secundarios que más preocupan a las mujeres jóvenes diagnosticadas de un cáncer de mama.

La información adecuada sobre este efecto secundario de los tratamientos por parte del oncólogo y el asesoramiento precoz, remitiéndolas a unidades especializadas de preservación de la fertilidad, es fundamental.

¿Cómo estimar la reserva ovárica en las pacientes con cáncer de mama?

- La amenorrea es generalmente el objetivo primario en la mayoría de los estudios porque es fácil de reportar, aunque es un predictor imperfecto del riesgo de infertilidad.
- La estimación de la reserva ovárica de una mujer es difícil de determinar. Se realiza a través de marcadores de reserva ovárica, como el recuento de folículos antrales y los niveles de hormona antimulleriana (HAM), siendo el valor predictivo de gestación de estos marcadores incierto.
- El significado de la HAM antes de un tratamiento gonadotóxico y su correlación con los niveles posteriores y con el riesgo de fallo ovárico es controvertido, siendo necesarios más estudios que lo corroboren.

¿Qué factores influyen en la pérdida de la fertilidad y en la posibilidad de recuperación de la misma?

El porcentaje de infertilidad y su recuperación depende de (631):

- Edad
- Estado de fertilidad antes del tratamiento
- Tipo de quimioterapia y dosis recibida

Gonadotoxicidad de los tratamientos del cáncer de mama

Tabla 100. Riesgo de esterilidad asociado a los tratamientos del cáncer de mama. Tabla elaborada por el autor y basada en Poorvu et al. 2019 (632).

Riesgo bajo (<25 % dismiución de la probabilidad de embarazo o aumento del riesgo de infertilidad)
Riesgo intermedio (25-75 % dismiución de la probabilidad de embarazo o aumento del riesgo de infertilidad)
Riesgo alto (>75 % dismiución de la probabilidad de embarazo o aumento del riesgo de infertilidad)

Tratamiento	Impacto en la fertilidad
AC x 4 en mujeres menores de 40	amenorrea
AC- T en mujeres menores de 40	amenorrea
AC x 4 en mujeres mayores de 40	amenorrea
AC –T en mujeres mayores de 40	amenorrea
FEC, FAC en mujeres menores de 30	amenorrhea
FEC, FAC en mujeres entre 30-39	amenorrea
Cisplatin > 600 mg/m2	amenorrea
Cisplatin < 600 mg/m2	amenorrea
Carboplatin	amenorrea
Tamoxifen	Embarazo/amenorrhea
TC, TAC	amenorrea
Trastuzumab	amenorrea
HCT conditioning (chemotherapyand/or TBI)	Pregnancy/gonadal insuficiency
Pelvic radiation	Pregnancy/gonadal insuficiency
Ifosfamide	amenorrhea
Actinomicina D	amenorrhea
Metotrexate	amenorrhea

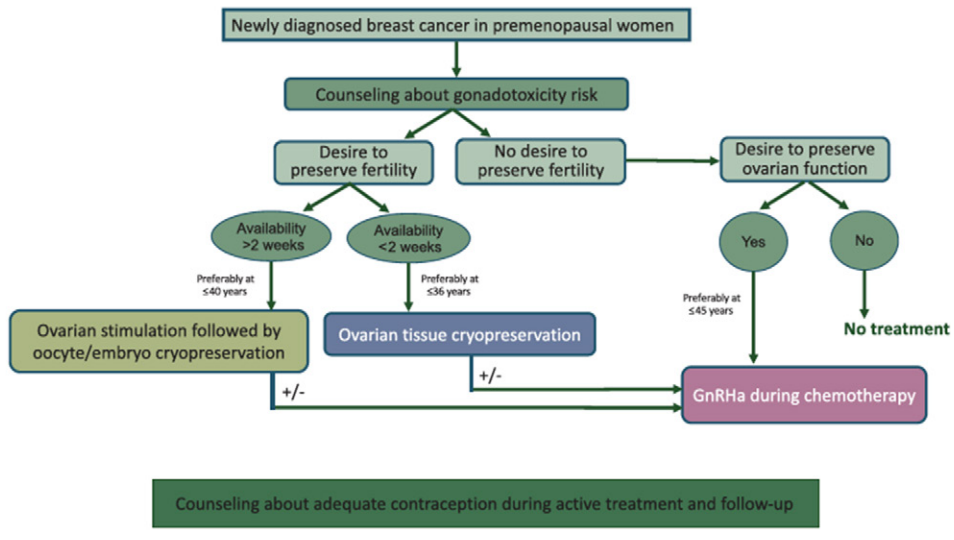
¿De qué técnicas disponemos para preservar la fertilidad en las pacientes con cáncer de mama?

Existen diferentes métodos y técnicas descritos en la literatura para preservar la fertilidad en pacientes jóvenes con CM. Cada método tiene ventajas e inconvenientes relacionados con sus tasas de éxito, el tiempo que se puede retrasar el tratamiento, la necesidad de estimulación ovárica, la necesidad de esperma y el riesgo de reintroducir células malignas.

- La vitrificación de ovocitos es la técnica de elección para preservar la fertilidad en pacientes con cáncer de mama si se dispone de tiempo para la estimulación ovárica. No se ha observado un aumento del riesgo de recurrencia tras la estimulación ovárica con gonadotrofinas y letrozol (633).

- La criopreservación de corteza ovárica se indicaría en aquellos casos en los que no se dispone de tiempo para la estimulación. Si se sospecha de un cáncer hereditario, la utilización de esta técnica es más controvertida.
- Las principales sociedades médicas [American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO) y Sociedad Española de Oncología Médica (SEOM)] no recomiendan la aplicación de agonistas de la GnRH como única técnica de preservación de fertilidad (634, 635, 636) dada la insuficiente evidencia en cuanto a su efectividad. Aunque sí puede ser una opción en pacientes con cáncer de mama y receptores hormonales negativos en las que no se contemplen otras técnicas según los datos del ensayo POEMS (637).
- La hormonoterapia adyuvante en cáncer de mama no compromete la fertilidad, pero la duración de esta hace que algunas pacientes no tengan posibilidades de embarazo tras finalizarla. Los resultados del estudio POSITIVE, que analiza si interrumpir temporalmente la terapia endocrina adyuvante con el fin de quedar embarazada aumenta el riesgo de recaída en pacientes jóvenes con cáncer de mama luminal, dilucidará si es posible utilizar esta estrategia (638).

Figura 43. Algoritmo de preservación de la fertilidad en pacientes con cáncer de mama. ***Basada en Gardino S.L. et al. (639).***



¿El embarazo tras el tratamiento de un cáncer de mama es seguro?

El embarazo no aumenta el riesgo de recaída o mortalidad en las pacientes con cáncer de mama, independientemente del status de los receptores hormonales (640).

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