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Cáncer de mama avanzado (I)

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Conventional-Dose Chemotherapy Compared with High-Dose Chemotherapy plus Autologous Hematopoietic Stem-Cell Transplantation for Metastatic Breast Cancer

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The New England Journal of Medicine 2000; 342: 1069-1072

ABSTRACT

Background We conducted a randomized trial in which we compared high-dose chemotherapy plus hematopoietic stem-cell rescue with a prolonged course of monthly conventional-dose chemotherapy in women with metastatic breast cancer.

Methods Women 18 to 60 years of age who had metastatic breast cancer received four to six cycles of standard combination chemotherapy. Patients who had a complete or partial response to induction chemotherapy were then randomly assigned to receive either a single course of high doses of carboplatin, thiotepa, and cyclophosphamide plus transplantation of autologous hematopoietic stem cells or up to 24 cycles of cyclophosphamide, methotrexate, and fluorouracil in conventional doses. The primary end point was survival.

Results The median follow-up was 37 months. Of 553 patients who enrolled in the study, 58 had a complete response to induction chemotherapy and 252 had a partial response. Of these, 110 patients were assigned to receive high-dose chemotherapy plus hematopoietic stem cells and 89 were assigned to receive conventional-dose chemotherapy. In an intention-to-treat analysis, we found no significant difference in survival overall at three years between the two treatment groups (32 percent in the transplantation group and 38 percent in the conventional-chemotherapy group). There was no significant difference between the two treatments in the median time to progression of the disease (9.6 months for high-dose chemotherapy plus hematopoietic stem cells and 9.0 months for conventional-dose chemotherapy).

Conclusions As compared with maintenance chemotherapy in conventional doses, high-dose chemotherapy plus autologous stem-cell transplantation soon after the induction of a complete or partial remission with conventional-dose chemotherapy does not improve survival in women with metastatic breast cancer.

COMENTARIO

Este estudio exploró, de forma prospectiva, el papel de la quimioterapia de intensificación como maniobra de consolidación tras la obtención de una remisión parcial o completa tras quimioterapia convencional para el cáncer de mama avanzado. El ensayo planificó la administración de quimioterapia intensiva tras 4-6 ciclos de quimioterapia convencional, y lo comparó con la administración de quimioterapia con el esquema CMF hasta progresión o un máximo de 24 ciclos. El objetivo primario de este estudio era comparar la supervivencia, el tiempo libre de progresión y la toxicidad.

Los resultados de este estudio, con una mediana de seguimiento de mas de tres años no se detectó ninguna diferencia entre ambas opciones de tratamiento así como tampoco se observó un incremento de mortalidad en la rama de tratamiento intensivo.

Estas observaciones de este estudio aletorizado asociadas a los datos obtenidos en otros estudios sugirieron la ausencia de eficacia de la quimioterapia intensiva como maniobra de consolidación tras obtener una remisión en el manejo terapéutico del cáncer de mama diseminado.

Accelerated-Intensified Cyclophosphamide, Epirubicin, and Fluorouracil (CEF) Compared With Standard CEF in Metastatic Breast Cancer Patients: Results of a Multicenter, Randomized Phase III Study of the Italian Gruppo Oncologico Nord-Ouest–Mammella Inter Gruppo Group

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Journal Clinical Oncology 2001; 19: 2213-2221

PURPOSE: To evaluate whether an accelerated-intensified cyclophosphamide, epirubicin, and fluorouracil (CEF) chemotherapy regimen with the support of granulocyte colony-stimulating factor (G-CSF) induces a higher activity and efficacy compared with standard CEF in metastatic breast cancer patients.

PATIENTS AND METHODS: Stage IV breast cancer patients were randomized to receive as first-line chemotherapy either standard CEF (cyclophosphamide 600 mg/m^2, epirubicin 60 mg/m^2, and fluorouracil 600 mg/m^2) administered every 21 days (CEF21) or accelerated-intensified CEF (cyclophosphamide 1,000 mg/m^2, epirubicin 80 mg/m^2, and fluorouracil 600 mg/m^2) administered every 14 days (HD-CEF14) with the support of G-CSF. Treatment was administered for eight cycles.

RESULTS: A total of 151 patients were randomized (74 patients on the CEF21 arm and 77 on the HD-CEF14 arm). In both arms, the median number of administered cycles was eight. The dose-intensity actually administered was 93% and 86% of that planned, in CEF21- and HD-CEF14–treated patients, respectively. Compared with the CEF21 arm, the dose-intensity increase in the HD-CEF14 arm was 80%. Both nonhematologic and hematologic toxicities were higher in the HD-CEF14 arm than in the CEF21 arm. During chemotherapy, four deaths occurred in the HD-CEF14 arm. No difference in overall response rate (complete plus partial responses) was observed: 49% and 51% in the CEF21 and HD-CEF14 arms, respectively (P = .94). A slightly non–statistically significant higher percentage of complete response was observed in the HD-CEF14 arm (20% v 15%). No difference in efficacy was observed. The median time to progression was 14.3 and 12.8 months in the CEF21 and HD-CEF14 arms, respectively (P = .69). Median overall survival was 32.7 and 27.2 months in the CEF21 and HD-CEF14 arms, respectively (P = .16).

CONCLUSION: In metastatic breast cancer patients, an 80% increase in dose-intensity of the CEF regimen, obtained by both acceleration and dose intensification, does not improve the activity and the efficacy compared with a standard dose-intensity CEF regimen.

COMENTARIO

En este estudio se plantea la hipótesis referente a si el aumento en la densidad de dosis conlleva una mejoría en el beneficio clínico de las pacientes afectas de un cáncer de mama diseminado. En este ensayo clínico se aleatorizó a las enfermas a recibir quimioterapia con el esquema CEF cada 21 días o bien cada 14 días con la misma dosis de epirubicina de 80 mg/m^2 pero con tratamiento de soporte con G-CSF durante 10 días. Los resultados de este estudio mostraron que la administración de un esquema CEF acelerado no se asociaba con una mayor eficacia, medida con los parámetros de índice de respuesta, tiempo libre de progresión y supervivencia. Por otra parte el esquema de tratamiento intensivo se asoció con una mayor tasa de mortalidad relacionada con el tratamiento.

Este estudio se diseñó con la expectativa de detectar una diferencia en índice de respuesta de un 25% y un incremento en la mediana del tiempo libre de progresión de cinco meses y se estimó que el tamaño muestral debía ser de 150 pacientes. Es probable que la asunción de un objetivo menos exigente permitiría intuir alguna diferencia, pero precisaría de un estudio con un mayor número de casos.

En resumen, los resultados de este estudio revelan que un incremento de la densidad de la dosis de forma global no conlleva un incremento del beneficio clínico. Estas observaciones asociadas a las obtenidas en algunos ensayos clínicos de quimioterapia intensiva han permitido descartar la utilización de dosis altas de quimioterapia en el tratamiento paliativo del cáncer de mama.

Multicenter Randomized Trial Comparing Sequential With Concomitant Administration of Doxorubicin and Docetaxel As First-Line Treatment of Metastatic Breast Cancer: A Spanish Breast Cancer Research Group (GEICAM-9903) Phase III Study

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Journal of Clinical Oncology 2004; 22:2587-2593

ABSTRACT

PURPOSE: This randomized, multicenter, phase III trial evaluated whether sequential doxorubicin and docetaxel (A" src="/math/rarr.gif" border=0T) reduced hematological toxicity, especially febrile neutropenia, compared with concomitant (AT) administration as first-line chemotherapy in metastatic breast cancer (MBC).

PATIENTS AND METHODS: One hundred forty-four patients were randomly assigned to receive three cycles of doxorubicin 75 mg/m^2 every 21 days followed by three cycles of docetaxel 100

mg/m², every 21 days (A" src="/math/rarr.gif" border=0T) or six cycles of the combination doxorubicin 50 mg/m² and docetaxel 75 mg/m² (AT) every 21 days. Patients previously treated with anthracyclines received two cycles of doxorubicin followed by four cycles of docetaxel (A" src="/math/rarr.gif" border=0T), or three cycles of AT followed by three cycles of docetaxel 100 mg/m² every 21 days.

RESULTS: Febrile neutropenia was less common in the A" src="/math/rarr.gif" border=0T arm (29.3% of patients, 6.9% of cycles) compared with the AT arm (47.8% of patients, 14.8% of cycles; P = .02 and P = .0004, respectively). Asthenia, diarrhea, and fever occurred more frequently in the AT arm. The overall responses rates were 61% in the A" src="/math/rarr.gif" border=0T arm (95% CI, 50% to 72%) and 51% in the AT arm (95% CI, 39% to 63%). The median duration of response was 8.7 months (A" src="/math/rarr.gif" border=0T) and 7.6 months (AT); the median time to progression was 10.5 months (A" src="/math/rarr.gif" border=0T) and 9.2 months (AT); the median overall survival was 22.3 months (A" src="/math/rarr.gif" border=0T) and 21.8 months (AT); and no significant differences were found.

CONCLUSION: A" src="/math/rarr.gif" border=0T significantly reduced febrile neutropenia compared with AT in MBC patients and maintains comparable antitumoral efficacy. A" src="/math/rarr.gif" border=0T represents a valid option for the treatment of MBC.

COMENTARIO

Este estudio se diseñó con el objetivo primario de demostrar que la administración secuencial de dos fármacos muy activos para el tratamiento del cáncer de mama metastásico como son la adriamicina y el docetaxel, inducía un menor índice de neutropenias febriles. Este objetivo quedó claramente demostrado. Al mismo tiempo, se observó que el índice de respuesta objetiva y la mediana del tiempo libre de progresión no fueron significativamente peores en aquellas enfermas que recibieron un tratamiento secuencial en comparación con aquellas que recibieron el tratamiento de forma concomitante. En resumen, los resultados de este estudio muestran que la administración secuencial de quimioterapia permite mejorar la tolerancia de las enfermas sin que ello conlleve una pérdida significativa de la actividad antitumoral, si bien este aspecto debe ser reforzado mediante los resultados de estudios aleatorizados expresamente diseñados para explorar este punto.

Second and subsequent lines of chemotherapy for metastatic breast cancer: what did we learn in the last two decades?

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Received 22 August 2001; revised 22 October 2001; accepted 15 November 2001.

Annals of Oncology 2002; 13: 197-207

ABSTRACT

'It matters not how long we live, but how.' . Festus, Philip James Bailey

Despite almost 30 years of clinical cancer research, the true impact of second and subsequent lines of chemotherapy on the outcome of metastatic breast cancer patients, especially on the duration of survival, is still unknown. In the virtually incurable metastatic setting, issues like quality of life and patients' preferences gain particular relevance. At the turn of the century, in-depth rethinking of the design of clinical trials run in this challenging disease setting appears to be warranted.

Key words: breast cancer, metastatic, quality of life, second line.

COMENTARIO

Este es un artículo de revisión referente al tratamiento con quimioterapia de segunda línea en el cáncer de mama diseminado. En

este trabajo se revisan las diferentes opciones terapéuticas, analizando su beneficio en términos de eficacia, prolongación del intervalo libre de progresión, supervivencia e impacto en la calidad de vida de las enfermas. Plantea un conjunto de reflexiones interesantes referentes a las tendencias actuales en el tratamiento y al nivel de evidencia que existe respecto a las mismas.

Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2

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The New England Journal of Medicine 2001; 344: 783-792

ABSTRACT

Background The HER2 gene, which encodes the growth factor receptor HER2, is amplified and HER2 is overexpressed in 25 to 30 percent of breast cancers, increasing the aggressiveness of the tumor.

Methods We evaluated the efficacy and safety of trastuzumab, a recombinant monoclonal antibody against HER2, in women with metastatic breast cancer that overexpressed HER2. We randomly assigned 234 patients to receive standard chemotherapy alone and 235 patients to receive standard chemotherapy plus trastuzumab. Patients who had not previously received adjuvant (postoperative) therapy with an anthracycline were treated with doxorubicin (or epirubicin in the case of 36 women) and cyclophosphamide with (143 women) or without trastuzumab (138 women). Patients who had previously received adjuvant anthracycline were treated with paclitaxel alone (96 women) or paclitaxel with trastuzumab (92 women).

Results The addition of trastuzumab to chemotherapy was associated with a longer time to disease progression (median, 7.4 vs. 4.6 months; P<0.001), a higher rate of objective response (50 percent vs. 32 percent, P<0.001), a longer duration of response (median, 9.1 vs. 6.1 months; P<0.001), a lower rate of death at 1 year (22 percent vs. 33 percent, P=0.008), longer survival (median survival, 25.1 vs. 20.3 months; P=0.046), and a 20 percent reduction in the risk of death. The most important adverse event was cardiac dysfunction, which occurred in 27 percent of the group given an anthracycline, cyclophosphamide, and trastuzumab; 8 percent of the group given an anthracycline and cyclophosphamide alone; 13 percent of the group given paclitaxel and trastuzumab; and 1 percent of the group given paclitaxel alone. Although the cardiotoxicity was potentially severe and, in some cases, life-threatening, the symptoms generally improved with standard medical management.

Conclusions Trastuzumab increases the clinical benefit of first-line chemotherapy in metastatic breast cancer that overexpresses HER2.

COMENTARIO

Este estudio es de gran importancia porque demostró por primera vez en un ensayo clínico aleatorizado la sinergia entre la quimioterapia y el trastuzumab en las pacientes con un tumor avanzado de mama con sobrexpresión del oncogen c-erbB-2. En efecto, la combinación de quimioterapia y trastuzumab presentó un incremento del beneficio clínico en todas sus dimensiones: aumento de la mediana del tiempo libre de progresión, el índice de respuesta, la mediana de la duración de la respuesta y la mediana de la supervivencia.

Sin embargo, en este estudio se detectó un incremento del riesgo de toxicidad cardíaca en las enfermas que recibieron trastuzumab y antraciclinas, en comparación con aquellas pacientes que habían recibido paclitaxel, a pesar de que el índice de respuesta objetiva fue discretamente superior en aquellos casos que recibieron inicialmente antracilinas.

Este estudio en definitiva significó un avance notable y fue la confirmación de observaciones iniciales que apoyaban el sinergismo de una terapia biológica dirigida a una diana terapéutica claramente identificada como es la amplificación del oncogen c-erbB-2 y la quimioterapia.