三陰性乳癌晚期轉移

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Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer

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全世界最好的雜誌,新英格蘭雜誌, N E J M， 2022 年 7 月 21 日，發表了有關乳癌，三陰性乳癌 ,晚期三陰性乳癌 ,轉移性乳癌三陰性 ,使用化學治療加上免疫治療藥物, Pembrolizumab, Merck 默克藥廠的藥, 這個是臨床三期的實驗, 無復發的存活率比單獨使用化學治療有較好的效果，主要用於 PD-L1 和 CPS(combined positive score)陽性的細胞, 研究是只要是局部晚期或者是局部復發的病人或者是不能夠開刀或者是轉移性的生陰性乳癌給予免疫治療藥 Pembrolizumab200 mg, 每三周再搭配化學治療,(np-albumin-bound paclitaxel, paclitaxel, gemcitabine- carboplatin) 可以比較他主要的研究主要是要看無復發的存活期是否， 第二個是想要看整體的存活，病人有 PD-L1 或者是 C P S 有大一時的病人或者是更多的這個族群中間是不是能夠看到有差異,比較 PD-L1 陽性的病人, CPS 只有一到五或者是>10 的病人, 有特別的差別那,總共收入了 847 個病, 566 個就是化學治療藥物加上免疫化學治療藥物, 281 個病人只有單單做化療加上安慰劑就是沒有打鏢靶藥物, 平均的追蹤 44.1 個月在 C P S>10 的平均的存活率是 23 個月再有加上化療加上免疫化學治療藥物, 只有化學藥物的那個族群是只有 16.1 個月, 如果是 CPS-1 的族群中間他的存活率是 17.6 個月，比上 16 個月，整個長期平均整體存活率是 17.2 個月比上 15.5 個月，不良化學治療化學反應第三第四第五級的時候在免疫治療加上化學治療藥物這個族群有 68.1 percent 的發生，化學治療組的 66.9 的機率發生，免疫治療加上化學治療有 0.4 percent 死亡率，化學治療加上安慰劑的組沒有沒有死亡的 (KEYNOTE-1355 研究)

Pembrolizumab（Keytruda）免疫檢查點抑制劑(２０１８國家衛生院電子報)

癌症免疫療法（immuno-oncology therapy，簡稱 IO）

Pembrolizumab（簡稱 Pembro；原名為 MK-3475 或 lambrolizumab；商品名為 Keytruda）為一種人源化的單株抗體，具有開啟 T 細胞被「關閉」的程序性死亡第一型蛋白（programmed cell death protein 1；簡稱 PD-1）的效果。

最為知名的案例之一是高齡 90 歲美國前總統卡特（Jimmy Carter），診斷罹患黑色素瘤並已擴散至腦部，經由 Keytruda 治療後癌細胞業已完全消失；因而公認 Keytruda 為近期最具潛力的癌症免疫治療藥物。

默沙東藥廠（Merck & Co., Inc.；簡稱 Merck，在美國及加拿大以外的地區則簡稱 MSD）。

傳奇藥品「沙利竇邁（thalidomide）」曾經惡名昭彰 ,1960 年代一起「海豹肢畸形（phocomelia）」的重大藥害事件；然而在藥理方面的突破卻扭轉了沙利竇邁的命運。Takumi Ito 博士及其同僚於 2010 年報導沙利竇邁會與蛋白質 cereblon（簡稱 CRBN）結合，並能抑制 CRBN 的酵素活性。更進一步的研究發現「來那度胺（lenalidomide）」是透過跟 CRBN 的結合能力而誘導在多發性骨髓瘤中非常重要的轉錄因子 Ikaros 和 Aiolos 的泛素化和降解（ubiquitination and degradation）。

新興的藥物化學領域：蛋白裂解靶向嵌合體（PROteolysis TArgeting Chimeras；簡稱 PROTAC）技術，從而促進了蛋白降解藥物的開發

免疫腫瘤學的發展, 1992 年日本京都大學 Tasuku Honjo（本庶 佑）教授首先發現 PD-1 蛋白，由 2002 年當時任職於美國梅奧診所（Mayo Clinics）的陳列平教授（現為耶魯大學醫學院教授）研究證實 PD-1 為 T 細胞上的一種抑制性受體。接著，2003 年荷蘭歐加農（Organon）製藥公司，為擴充業務範圍而選擇開發抗體藥物，依據公司導向設定以 PD-1 為標的著手開發 PD-1 激活劑，期望藉由開發激活受體的抗體藥物關閉 T 細胞，進而抑制自體免疫性疾病患者過度旺盛的免疫反應。

Abstract

BACKGROUND

In an interim analysis of this phase 3 trial, the addition of pembrolizumab to chemotherapy resulted in longer progression-free survival than chemotherapy alone among patients with advanced triple-negative breast cancer whose tumors expressed programmed death ligand 1 (PD-L1) with a combined positive score (CPS; the number of PD-L1–staining tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells, multiplied by 100) of 10 or more. The results of the final analysis of overall survival have not been reported.

METHODS

We randomly assigned patients with previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer in a 2:1 ratio to receive pembrolizumab (200 mg) every 3 weeks plus the investigator's choice of chemotherapy (nanoparticle albumin-bound paclitaxel, paclitaxel, or gemcitabine–carboplatin) or placebo plus chemotherapy. The primary end points were progression-free survival (reported previously) and overall survival among patients whose tumors expressed PD-L1 with a CPS of 10 or more (the CPS-10 subgroup), among patients whose tumors expressed PD-L1 with a CPS of 1 or more (the CPS-1 subgroup), and in the intention-to-treat population. Safety was also assessed.

RESULTS

A total of 847 patients underwent randomization: 566 were assigned to the pembrolizumab–chemotherapy group, and 281 to the placebo–chemotherapy group. The median follow-up was 44.1 months. In the CPS-10 subgroup, the median overall survival was 23.0 months in the pembrolizumab–chemotherapy group and 16.1 months in the placebo–chemotherapy group (hazard ratio for death, 0.73; 95% confidence interval [CI], 0.55 to 0.95; two-sided P=0.0185 [criterion for significance met]); in the CPS-1 subgroup, the median overall survival was 17.6 and 16.0 months in the two groups, respectively (hazard ratio, 0.86; 95% CI, 0.72 to 1.04; two-sided P=0.1125 [not significant]); and in the intention-to-treat population, the median overall survival was 17.2 and 15.5 months, respectively (hazard ratio, 0.89; 95% CI, 0.76 to 1.05 [significance not tested]). Adverse events of grade 3, 4, or 5 that were related to the trial regimen occurred in 68.1% of the patients in the pembrolizumab–chemotherapy group and in 66.9% in the placebo–chemotherapy group, including death in 0.4% of the patients in the pembrolizumab–chemotherapy group and in no patients in the placebo–chemotherapy group.

CONCLUSIONS

Among patients with advanced triple-negative breast cancer whose tumors expressed PD-L1 with a CPS of 10 or more, the addition of pembrolizumab to chemotherapy resulted in significantly longer overall survival than chemotherapy alone. (Funded by Merck Sharp and Dohme; KEYNOTE-355

關鍵字　晚期三陰性乳癌，免疫治療，Pembrolizumab（Keytruda）免疫檢查點抑制劑，癌症免疫療法（immuno-oncology therapy，簡稱 IO）

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