Trastuzumab in inflammatory breast cancer

Inflammatory breast cancer (IBC) is associated with poor survival, specifically hormone receptor-negative subtype [1].

The dose-dense chemotherapy scheduling may be important in IBC as IBC is hyperproliferative, more often

epidermal growth factor receptor-2 positive (HER2+), and hormone receptor negative [2, 3]. Separately, trastuzumab modulates DNA–platinum adducts, thereby enhancing platinum efficacy. Collectively, we hypothesized that poor survival for IBC will improve with trastuzumab use with optimal chemotherapy in HER2+ IBC, similar to that seen in early breast cancer [4].

Of the prospective database 46 patients with HER2+ (a staining intensity of 3+ on the HercepTest or ≥2 amplification on FISH) breast cancer treated between 2003 and 2006, 16 patients had IBC with median age of 52. Follow-up data were analyzed on March 2008. Tumors were considered hormone receptor positive for estrogen and or progesterone receptor positivity at a cut-off of 10% for positivity.

Generally, patients were treated preoperatively with *in vivo* chemosensitivity-adapted two to four cycles of dose-dense doxorubicin–cyclophosphamide at 60 and 600 mg/m^2 (supported by granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor). This was followed by weekly paclitaxel [(cremophor–paclitaxel at 80 mg/m^2 (nine patients) or albumin-bound paclitaxel at 100 mg/m^2 (six patients)] and weekly carboplatin at area under the curve of 2, both 3 weeks on and 1 week off—one cycle, three to four cycles and 11–16 weekly concurrent trastuzumab at 4 mg/kg loading and 2 mg/kg maintenance (except two patients who received trastuzumab only postoperatively because of HER2 positivity detection in the residual tumor). Postoperatively, nine patients received trastuzumab, and four received hormonal modulation.

Significant toxic effects (National Cancer Institute Common Toxicity Criteria, version 2.0) included one patient with metastatic IBC died of thromboembolism after recovering from neutropenic sepsis following paclitaxel–carboplatin–trastuzumab (cirrhosis at autopsy, but no cancer), one developed neutropenic fever despite peg-filgrastim support with dose-dense doxorubicin-cyclophosphamide (AC). Grades 3–4 neuropathy, arthralgia or cardiac dysfunction or ejection fraction <50% or thrombocytopenia was not noted.

All patients (100%, 95% confidence interval 84% to 100%) achieved major clinical response. Pathologic complete response rates as function of tumor characteristics are shown in Table 1.

Median time of follow-up of surviving patients is 34 months. Progression-free, overall, and breast cancer-specific survival of all 16 patients (range 17–60 months) are 69% (11 of 16), 86% (13 of 16), and 89% (14 of 16), respectively. Of the five patients with stage IV IBC, two died of uncontrolled central nervous system (CNS) disease; third patient has uncontrolled CNS progression and fourth has systemic progression. Of the 10 patients with stage III or secondary IBC, PFS is 90% (nine of 10) and overall survival is 100% (10 of 10) at a median follow-up time of 34 months (range 24–60), with one patient having controlled systemic but uncontrolled CNS progression. Of the seven patients with stage III hormone receptor-negative subtype, six (86%) are progression free at a median follow-up of 43 months (range 24–60 months).

Doxorubicin–cyclophosphamide targets HER2-positive topoisomerase II coamplified cells and carboplatin–paclitaxel–trastuzumab additionally targets HER2-positive topoisomerase II normal or deleted cells; the sequential administration may have been optimal in a heterogeneous HER2-positive population. Pathologic complete response pattern in IBC paralleled the molecular phenotypes of breast cancer [5].

Importantly, for the patients with hormone receptor-negative IBC who historically have a median survival of 2 years, our results of 86% progression-free survival at a median follow-up of 43 months associated with high pathologic complete response is promising.

Table 1. Pathologic complete response rates as function of tumor characteristics

Tumor characteristic (n = 15)	pCR (%)	95% confidence interval
HER2+ (15)[a]	9 (60)[a]	30–80
HER2+/HR− (11), HER2+	8 (72)	40–97
HER2+/HR+ (4), luminal-B[a]	1 (25)	4–77
Stage		
Metastatic (5)	3 (60)	12–74
Locally recurrent (secondary IBC) (1)	1 (100)	0.05–72
Stage IIIB/IIIC (9)	5 (56)	21–86
Stage IIIB/IIIC/ secondary IBC (10)	6 (60)	26–89
Preoperative trastuzumab		
Yes (13)	9 (70)	39–91
No (2)	0 (0)	0–84
Anthracycline–cyclophosphamide cycles		
2–3 (10)	5 (50)	19–81
4 (5)	4 (80)	28–99

One patient with stage IV with underlying cirrhosis died of embolism (no evidence of residual invasive cancer in breast at autopsy) before treatment completion; thus 15 patients were assessable for pathologic response. In addition to nine patients who had pathologic complete response, three patients had ≤5 mm residual invasive cancer; therefore, 12 of 15 (80%) patients had tumor ≤5 mm; 12 of 15 (80%) patients had no residual lymph node involvement.
[a]Of the three of six HER2+ IBC patients who did not achieve pathologic complete response, two patients received trastuzumab postoperatively and one patient received two cycles of AC despite partial response to AC and completed two additional cycles of AC postoperatively.
IBC, inflammatory breast cancer.
pCR, pathologic complete response; HER2, epidermal growth factor receptor-2; HR, hormone receptor.

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