Introduction

The detection of circulating tumor DNA (ctDNA) during neoadjuvant therapy (NAT) may serve as an early indicator of emerging resistance and disease progression. In this study, we analyzed ctDNA from high-risk early breast cancer patients who received NAT and definitive surgery in the I-SPY 2 trial (NCT01042379). We hypothesized that ctDNA can serve as a biomarker of response and survival in this setting.

Methods

A personalized ctDNA test was designed to detect 18 patient-specific variants from whole exome sequencing of pretreatment tumor DNA from plasma in 67 high-risk early breast cancer patients who received NAC +/− investigational agent MK-2206 in the I-SPY 2 trial.

Results

• 73% of patients were ctDNA-positive at baseline. ctDNA positivity and levels were significantly associated with larger tumors and more aggressive tumor biology and subtypes (Figure 2).

• ctDNA levels during NAT decreased over time. Five ctDNA clearance patterns were observed (Figure 3).

• All eight patients who died and nine out of 10 patients who had distant recurrence had detectable ctDNA in at least one timepoint (Figure 4).

• Patients who remained ctDNA-negative at T1 were significantly more likely to have a non-pCR (83%) compared to those who cleared ctDNA (52%; OR: 4.33, P<0.01) (Figure 4).

• Patients who did not clear ctDNA had the worst survival compared to those who cleared ctDNA and remained ctDNA-negative. Interestingly, the non-pCR ctDNA-negative patients had similar risk of metastatic recurrence to those who achieved a pCR, while the 6 non-pCR ctDNA-positive patients had significantly increased risk of metastatic recurrence (Figure 5).

Conclusions

• Early clearance of ctDNA during NAT was significantly associated with increased likelihood of achieving a pCR.

• ctDNA at any point during NAT was associated with improved outcomes.

• ctDNA-negative patients were more likely to have complete response to treatment and a lower risk of distant recurrence.

• ctDNA status after neoadjuvant chemotherapy (T3) and response to treatment (pathological complete response, pCR).

• ctDNA-negative patients had similar risk of metastatic recurrence to those who achieved a pCR, while the 6 non-pCR ctDNA-positive patients had significantly increased risk of metastatic recurrence (Figure 5).

Patient Advocate’s Perspective

We are writing to support the application of this clinical study to help provide new treatment options for breast cancer patients. This research has the potential to improve survival outcomes and quality of life for breast cancer patients. The findings presented in this study emphasize the importance of ctDNA testing in the context of neoadjuvant therapy.

Acknowledgments

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References


