Background: To explain the bimodal pattern of hazard of relapse among early stage breast cancer patients, we propose that there exist two distinct phases of tumor cell dissemination: the first, early phase is stochastic, and the second, delayed phase is facilitated by perioperative surgical stimuli. Prior to the time of surgery, tumor cells may extravasate, resulting months later in a metastatic tumor. Circulating cancer cells and cells released as a result of surgery, produce what has been termed the late broad peak. If so, this would be the first such sighting.

Methods and Materials: In June 2010, Forget et al (2) reported data from a retrospective descriptive disease-free survival study of 327 consecutive patients comparing various perioperative analgesics and antiinflammatories (acetaminophen, ibuprofen, ketorolac, and ketamine) in one Belgian hospital and one surgical unit. Patients were treated with mastectomy and conventional adjuvant chemotherapy. Follow-up is average 27.3 months with range 13-44 months.

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Results and Discussion: NSAID ketorolac, a common surgical anti-inflammatory agent, was associated with significantly superior disease-free survival in the first 5 years after surgery. The expected prominent early peak of relapses is all but absent in the ketorolac (fig. 4, A), specifically, the relapse rate is approximately 4–6 fold. The few events in the ketorolac group show a small bump in the first 10 months and then slowly rise until the 36th month. Simulations of the two early relapse modes are shown in fig. 3. Using these data, we have been able to explain this bimodal pattern of previously unpredictable disease recurrence with this observation. This hypothesis include the high effectiveness of adjuvant chemotherapy, which probably resulted in high initial survival rates in patients who then had a significant disease-free survival.

Possible Mechanism: The transient systemic inflammation accompanying surgery could be part of the metastatic tumor seeding process and could have been effectively blocked by perioperative anti-inflammatory agents.

Results: Postoperative anti-inflammatory agents, when administered throughout the period of surgery, were associated with significantly superior disease-free survival in the first 5 years after surgery. The expected prominent early peak of relapses is all but absent in the ketorolac group, specifically, the relapse rate is approximately 4–6 fold. The few events in the ketorolac group show a small bump in the first 10 months and then slowly rise until the 36th month. Simulations of the two early relapse modes are shown in fig. 3. Using these data, we have been able to explain this bimodal pattern of previously unpredictable disease recurrence with this observation. This hypothesis include the high effectiveness of adjuvant chemotherapy, which probably resulted in high initial survival rates in patients who then had a significant disease-free survival.

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Discussion

Even with the insight of simulations, it is sometimes impossible to determine with certainty that surgery is the cause. If this is the case, the metastatic tumor process is established, and it is impossible to determine the exact time of surgery’s impact. While we do not yet know the exact time of surgery’s impact, we do know that the relapse rate is significantly reduced when the NSAID ketorolac is used perioperatively.

Possible Mechanism: The transient systemic inflammation accompanying surgery could be part of the metastatic tumor seeding process and could have been effectively blocked by perioperative anti-inflammatory agents.

Discussion

Our findings suggest that most relapses occurring within 1-4 years may be induced by the effects of breast cancer surgery. A possible mechanism is that the surgical inflammatory process, which is in the presence of circulating cancer cells and muscles released as a result of surgery, produces what has been called intraoperative metastatic activity.

We have found that peri-operative anti-inflammatory agents appear to abrogate the early hazard of recurrence and we estimate that such intervention could reduce breast cancer mortality by 25% to 50%.

High priority should be given to test this hypothesis in a randomized trial as it is implementable regardless of state of socioeconomic development because expensive drugs, modern imaging facilities and advanced pathology services are not particularly relevant to implementing this simple change.

Also as noted by Forget et al (15), the metastatic process in breast cancer outcome is due primarily to deaths within the first few years after diagnosis providing an additional motivation to test at the earliest opportunity what we report here.

Overall, our data support the position that circulating tumor cells are a reality. Surgical induction of inflammation is universal. Capillary leakage is enhanced and systemic inflammatory response syndromes are common. Even if an effective anti-inflammatory strategy may affect surgery-induced and possibly angiogenesis-mediated cancer spread. It shows a schematic description of what we suspect to be the mechanisms governing metastatic relapse from early breast cancer. Despite the significant progress made in understanding tumor angiogenesis, we are still far from being able to control or prevent these late relapses.

The most interesting part of this study is that the early relapse risk following surgery appeared to be significantly lower when ketorolac was used. This suggests that ketorolac may have a role in reducing the risk of early relapse following breast cancer surgery.

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