CORRESPONDENCE

Acceptance of Tamoxifen Chemoprevention by Physicians and Women at Risk

Tchou et al.[1] recently published a retrospective chart review of women choosing to receive tamoxifen for chemoprevention of breast carcinoma. One hundred thirty-seven women seeking risk counseling for breast carcinoma were offered tamoxifen for chemoprevention, and 57 (42%) chose to receive this agent. The authors found that a history of atypical hyperplasia or lobular carcinoma in situ (LCIS) and older age were significant predictors of being offered and accepting treatment with tamoxifen. The figures reported by Tchou et al. are in sharp contrast to the results reported by Port et al,[2] who found that 43 women with a 5-year risk of developing breast carcinoma $>$ 1.7% (as predicted by the Gail model) were given information regarding the benefits and risks of tamoxifen and that only 2 of these women (4.7%) chose to receive tamoxifen therapy.

These discrepancies in terms of acceptance rates may be attributable to the way in which information was provided. Despite the best intentions of physicians, it may be impossible to present information to patients in a truly unbiased fashion. A physician's description of a treatment and the strength of the recommendation,[3] in addition to the framing of information,[4] may influence patients. Although in these two previous studies, the authors state that they provided 'neutral risk counseling'[1] or 'neutral education sessions and literature',[2] this neutrality was not explicit, and some bias in favor or against tamoxifen use may have been present. The Tchou et al. study did not include the physician as a variable having a possible effect on the offering or acceptance of tamoxifen therapy.

In our own prospective study, which attempted to remove physician-related biases through the use of a standardized decision guide, only 6 of 41 women (14.6%) who had high-risk status (mean 5-year Gail risk, 3.4%; atypia rate, 61%) were willing to receive tamoxifen for chemoprevention, a figure that was intermediate relative to the Tchou et al. and Port et al. studies. Although information cannot be tailored specifically to the patient using the decision guide, generic information can be conveyed to introduce the concept of chemoprevention, and the issue can be explored further at the request of the patient.

We commend Tchou et al.[1] for offering more insight into the proportion of women expressing an interest in tamoxifen chemoprevention. There remain several challenges related to how to best identify and approach women who have an elevated risk of developing breast carcinoma (as routine screening using the Gail model is not recommended[5]) and how to best provide information on the small absolute benefits and the small but significant risks associated with tamoxifen use. The balance between the benefits and harms of tamoxifen use is a delicate one, and decisions regarding tamoxifen use are best made by informed patients who are free from the influence

of physician-related biases. The existing literature suggests that the issue of physician-related bias has not yet been addressed.

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Andrew McKay, M.D.
Steve Latosinsky, M.D.
Wanda Martin, M.N.
Health Sciences Centre
University of Manitoba
Winnipeg, Manitoba, Canada

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Granulocyte—Colony-Stimulating Factor (Filgrastim) may Overcome Imatinib-Induced Neutropenia in Patients with Chronic-Phase Myelogenous Leukemia

We read with interest the report by Quintas-Cardama et al.[1] on supportive growth factor therapy for imatinib-induced neutropenia in patients with chronic-phase chronic myelogenous leukemia (CML). The authors propose that the improved cytogenetic responses observed in the majority (62%) of patients with CML were correlated with an increased imatinib dose or an increased treatment duration, made possible by the normalization of absolute neutrophil counts via granulocyte–colony-stimulating factor (G-CSF) therapy. However, we believe that there is an alternative G-CSF–dependent explanation, which was alluded to but not discussed fully in that article, for the observed improvement in outcome.

Dormant primitive progenitors can be triggered to cycle in response to cytokines, including G-CSF.[2] G-CSF administration promotes rapid progression into S phase of initially quiescent primitive ($c\text{-}kit^+/Sca\text{-}1^+/lin^-$) murine progenitors.[3] Furthermore, G-CSF receptor (*GCSFR*) transcripts are detectable in normal human $CD34^+/CD38^-$ cells at 2-fold higher levels compared with the more mature $CD34^+/CD38^+$ compartment.[4] In support of this hypothesis, we found significantly elevated *GCSFR* transcript levels in sorted subsets of quiescent primitive CML cells compared with their normal counterparts.[5]

These data suggest that CML hematopoietic progenitors are primed to respond to exogenous growth factors. The expectation, therefore, is that the response to imatinib would improve in the presence of growth factor support, due to the cycling of primitive leukemic progenitors and the escape of cells from the imatinib-insensitive quiescent state.[6] In fact, induction therapy involving G-CSF and cytarabine has been shown to improve overall and disease-free survival for patients with standard-risk acute myelogenous leukemia.[7]

It is our belief that the second possible explanation for the observed improvement in cytogenetic profiles for patients with CML who received supportive G-CSF therapy for neutropenia involves the sensitization of leukemia cells to imatinib chemotherapy. In other words, irrespective of imatinib dose escalation, the introduction of G-CSF therapy could have yielded improved responses, although this would require verification in a controlled clinical trial.

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Heather G. Jørgensen, Ph.D.
Mhairi Copland, M.D.
Tessa L. Holyoake, M.D., Ph.D.
Division of Cancer Sciences and Molecular Pathology
Faculty of Medicine
University of Glasgow
Glasgow, United Kingdom

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Familial Risk and Clustering of Nasopharyngeal Carcinoma in Guangdong, China

We read with interest the recent article by Jia et al.[1] on familial risk of cancer and the clustering of nasopharyngeal carcinoma (NPC). The authors reported that first-degree relatives of patients with NPC had a dramatically decreased risk of developing malignant disease in general (standardized incidence ratio [SIR], 0.35), and carcinoma of the lung (SIR, 0.24), carcinoma of the esophagus (SIR, 0.23), and carcinoma of the breast (SIR, 0.08) in particular. The results are striking, as, to our knowledge, protective effects of this magnitude have not been observed before among relatives of individuals with cancer. The results of the study were derived from a large group of patients with NPC. However, the method used deserves comment, as the study design suggests limitations not addressed in the article.

First, the authors obtained information on malignant diseases in relatives from Guangdong by interviewing probands. Thus, dates of birth, occurrences of malignancies, dates of diagnosis, and dates and causes of death were based on recall. This information was then compared with data from the Hong Kong Cancer Registry, which includes information from hospitals, laboratory and pathologic departments, death certificates, and discharge summaries.[2] It is therefore highly questionable as to whether the two data sources were comparable in terms of their completeness.

Second, the authors estimated SIRs by applying stratum-specific incidence rates from Hong Kong for the period 1988–1992 to the corresponding numbers of person-years in the study cohort. However, the observation time for relatives was calculated from the time of birth to the date of death, diagnosis, or interview, which means that the observation period for relatives could begin a lifetime earlier. Comparing cancer rates across such a time span is difficult, as incidences will have changed significantly over the period in question. For example, over the period 1973–1999, the age-adjusted rate of breast carcinoma in Hong Kong has increased considerably.[3] Therefore, instead of the desired comparison between relatives and the background population, a comparison between earlier and current cancer rates is achieved.

Both of these limitations easily could have led to the low estimates of cancer risk that were reported. Thus, the results of the study are inconclusive; exclusion of the possibility of an excess of malignancies other than NPC in these families is not reasonable based on the study design that was chosen. A more accurate estimation of risk among relatives could have been achieved by recruiting and interviewing a matching control group, an option that would have yielded the maximum benefit from this large and valuable data source.

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Jeppe Friborg, M.D.
Jan Wohlfahrt, M.Sc.
Mads Melbye, M.D., D.M.Sc.
Department of Epidemiology Research
Statens Serum Institut
Copenhagen, Denmark

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Author Reply

We thank Dr. Friborg and colleagues for their thoughtful comments on our recent article[1] in which we reported that "the SIRs for other malignancies examined in the Cantonese population were less

than 1 relative to the Hong Kong and Shanghai reference population."[2] Below, we discuss the two weaknesses related to this statement in terms of the statistical methods used in our analysis, as raised by Dr. Friborg.

First, Dr. Friborg and colleagues correctly point out that the information on malignant diseases in relatives was collected by interview with the probands and therefore was based on recall. They questioned whether the comparison between information based on recall and the data from the Hong Kong Cancer Registry was appropriate and whether the two data sources were comparable in terms of their completeness. To address this concern, we would like to reveal more details on how the data were collected.

For the purposes of quality control, we performed a secondary investigation of 100 pedigrees selected randomly from a cohort that included 2252 pedigrees. It is noteworthy that the interviewers for the second study were different from the ones who conducted the first interview with these 100 probands. The second interview team was composed of 14 medical students trained at the Cancer Center of Sun Yat-sen University (Guangzhou, China). These students visited all 100 probands at their residences. Although it was difficult to obtain complete data on information such as the precise date of diagnosis, we administered a detailed questionnaire that included items on clinicopathologic diagnosis, surgical history as a result of the malignancy, and whether the relatives had received either radiotherapy or chemotherapy. If the proband responded to one of the above four items in the affirmative, we coded his/her relative as a case. When we compared the results from both interviews using a chi-square test, no significant difference was found.

We interviewed only first-degree relatives ($n = 718$). In the study population examined, first-degree relatives and probands tend to live in similar areas. Therefore, the information we collected is likely to be more reliable than that provided by more distantly related relatives. We believe that it is reasonable to use the Hong Kong Cancer Registry as a reference population, although we indicated in our previous publication that the comparison was rather crude. Our goal is to eventually establish a cancer registry that encompasses all areas of Guangzhou.

We agree with Dr. Friborg that, due to the extended period covered by our comparisons, we are likely to have overestimated the risks of other malignancies among relatives of probands. Increases in lung and breast carcinoma risk over the last 20–30 years could have led to this overestimation and, therefore, to an underestimation of the standardized incidence ratio. Therefore, our results regarding other malignancies must be interpreted with caution. We believe that our estimation of nasopharyngeal carcinoma (NPC) risk among relatives is accurate, because the temporal trend in incidence runs counter to the observed risk. Over the last 30 years, the NPC rate appears to have remained stable according to the Sihui Cancer registry. (Sihui is known as a high-risk area for NPC in Guangzhou.)

Finally, we have completed a matched case–control study involving the same study cohort as the one discussed here. We hope to provide a more accurate estimation of the risk of other malignancies among relatives of probands in the near future.

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Wei-Hua Jia, M.D., Ph.D.
Yi-Xin Zeng, M.D., Ph.D.
Department of Experimental Research
Sun Yat-Sen University Cancer Center
Guangzhou, China
Yin Yao Shugart, Ph.D.
Department of Epidemiology
Bloomberg School of Public Health
Johns Hopkins University
Baltimore, Maryland

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