Array Comparative Genomic Hybridization and Cytogenetic Analysis in Pediatric Acute Leukemias

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KEY WORDS
Acute lymphoblastic leukemia, chromosomes, microarray, acgh


E-JOURNAL LINKED ABSTRACT
Most patients with acute lymphoblastic leukemia (ALL) are reported to have acquired chromosomal abnormalities in their leukemic bone marrow cells. Many established chromosome rearrangements have been described, and their associations with specific clinical, biologic, and prognostic features are well defined. However, approximately 30% of pediatric and 50% of adult patients with ALL do not have cytogenetic abnormalities of clinical significance. Despite significant improvements in outcome for pediatric ALL, therapy fails in approximately 25% of patients, and these failures often occur unpredictably in patients with a favorable prognosis and “good” cytogenetics at diagnosis.

Karyotype analysis in hematologic malignancies, although genome-wide, is well known to have limitations because of altered cell kinetics (mitotic rate), a propensity of leukemic blasts in culture to undergo apoptosis, overgrowth by normal cells, and the presence of poor-quality chromosomes in the abnormal clone. In array comparative genomic hybridization (acgh, “microarray”), genomic resolution is greatly increased over that in classical cytogenetics. Microarray, a powerful tool that uses DNA in the analysis of unbalanced chromosome rearrangements such as copy number gains and losses, is the method of choice when the mitotic index is low and the quality of metaphases is suboptimal. The copy number profile obtained by microarray is often called the “molecular karyotype.” However, microarray cannot detect balanced chromosome rearrangements such as translocations or inversions that have no copy number changes, making the continued routine use of conventional cytogenetics essential.

In the present study, microarray was retrospectively applied to 9 cases of pediatric ALL with either initial high-risk features or at least 1 relapse. The conventional karyotype was compared with the microarray “molecular karyotype” to assess abnormalities as interpreted by classical cytogenetics. Microarray not only identified previously undetected chromosome losses and gains, but also showed discordances with several karyotypes interpreted by classical cytogenetics. This initial study has demonstrated that DNA microarray is a reliable method for the identification of cytogenetically visible and cryptic imbalances in pediatric ALL. The complementary use of acgh and conventional cytogenetics can provide further information about relevant and repeated mutations in ALL. Clinical analysis could then focus on the specific mutations, with impacts on diagnosis, prognosis, and treatment. Based on our experience with these 9 cases, we propose the following algorithm for the cytogenetic evaluation of hematologic malignancies:

1. Conventional karyotype
2. Complementary microarray analysis
3. If required, FISH (fluorescence in situ hybridization) analysis for microarray-identified abnormalities to confirm or revise conventional karyotype.

The complementary use of microarray and conventional cytogenetics would allow for more sensitive, comprehensive, and accurate analysis of the underlying genetic profile, with concomitant improvement in prognosis and treatment, not only for pediatric ALL, but for neoplastic disorders in general.

Survival and Treatment Patterns in Elderly Patients with Advanced Non-Small-Cell Lung Cancer in Manitoba

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Hepatic Arterial Infusion of Oxaliplatin and 5-Fluorouracil in Combination with Intravenous Cetuximab

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KEY WORDS
Hepatic, arterial, infusion, colorectal, liver metastases, cetuximab, oxaliplatin, remission


E-JOURNAL LINKED ABSTRACT
At diagnosis of a CT3N0M1 adenocarcinoma of the rectum with synchronous inoperable liver metastases, a 59-year-old man was treated with preoperative radiotherapy (5×5 Gy), followed by laparoscopy-assisted anterior resection of the rectum with total mesorectal excision. At the first postoperative evaluation, a new lung metastasis was detected. First-line chemotherapy with FOLFIRI [5-fluorouracil (5FU)–irinotecan–leucovorin] resulted in a transient stabilization of the metastatic liver disease. At progression, oxaliplatin and 5FU–folinic acid were administered by intrahepatic arterial infusion (HAI), in combination with intravenous cetuximab. A partial radiologic response was obtained, with complete metabolic response on fluorodeoxyglucose positron-emission tomography (FDG-PET) and normalization of carcinoembryonic antigen values. This solitary lung metastasis was sequentially treated by radiotherapy and resection. Six years after the initial diagnosis, this patient remains free from progression, with residual cystic remnants of the liver metastases visible on conventional computed tomography imaging, but non-enhancing on FDG-PET.

The unexpected durable remission in this patient was obtained during treatment in a phase I study. The feasibility of combining cetuximab, a monoclonal antibody targeted to the epidermal growth factor receptor (EGFR), with combination chemotherapy by HAI was recently published.

In the neoadjuvant setting, HAI was associated with superior survival and better physical functioning than was obtained with systemic administration (24.4 months vs. 20 months, p = 0.0034) during a comparison of a fluoropyrimidine with HAI in single-agent cytotoxic therapy, which did not unequivocally demonstrate superiority in terms of survival compared with the systemic route of administration. The median overall survival observed in the experimental arms of two recently conducted phase III trials using FOLFIRI plus cetuximab of FOLFOX (5FU–leucovorin–oxaliplatin) plus...
bevacizumab were 24.9% (wild type KRAS patients only) and 21.3% respectively.

Patients with liver metastases from colorectal cancer have a poor survival prognosis when no R0 surgical resection of the LMS can be offered. Despite improvements in the activity of combination chemotherapy and of combinations with therapeutics targeting vascular endothelial growth factor of EGFR, most of the patients diagnosed with extrahepatic metastases and those with inoperable LMS cannot be offered cure and long-term disease control. At the time of writing, the patient reported here remains in complete remission in response to the combination of HAI chemotherapy (oxaliplatin–leucovorin–5FU) and an intravenous EGFR inhibitor (cetuximab, a monoclonal antibody with demonstrated activity against KRAS wild-type colorectal cancer). This case merits further investigation; combination therapy including HAI may open a promising era of tailored therapy in which only patients known to benefit will be treated.

Caring for Survivors of Breast Cancer: Perspective of the Primary Care Physician

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KEY WORDS
Breast cancer survivors, primary care physician perspective, follow-up cancer care, survivorship care plans


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Background and Objectives: The concept of survivorship care has received increased attention in the last several years, which may largely be a result of the increasing number of patients surviving breast cancer. In the Canadian province of British Columbia, survivors of breast cancer (SBC) are usually followed by their primary care physicians (PCP) after completion of active oncology treatment. The present study offers insight into PCP confidence in their ability to provide such care and explores potential ways to assist them in this aspect of their practice.

Methods: In British Columbia, typical practice is to discharge SBC to the care of their PCP in the first year after completion of active oncology treatment. A one-page, 31-item check box and open-answer questionnaire assessing perceptions and preferences about this aspect of practice was designed and mailed to 1000 PCP known to be following SBC in their practice. Questions addressed self-rated PCP confidence in the ability to provide follow-up care for SBC, preferences for the format and content of discharge communication from oncologists and preferred resources for obtaining information about breast cancer. Descriptive statistics and the Pearson chi-square test were used to summarize findings.

Results: A total of 587 PCP returned completed surveys (response rate: 59%). Discharge information deemed most useful in assisting PCP to manage SBC included: diagnosis and treatment summary, recommended follow-up protocol, and recommended adjuvant hormonal therapy. Preference for the format of discharge information was point form for 43% of respondents, detailed description for 19%, and both formats for 38%. PCP were most confident screening for recurrence and managing patient anxiety, and least confident in managing lymphedema and providing counseling on sex, body image, and family concerns. PCP following more SBC displayed higher confidence in managing the biomedical aspects of follow-up and in providing counselling about nutrition and exercise than those following fewer SBC. Respondents most commonly used online resources and continuing medical education seminars to access information about breast cancer.

Conclusions: The PCP providing follow-up care for SBC are confident managing most aspects of care. Discharge information that includes a record of diagnosis and care received, surveillance recommendations, and recommended hormonal therapy is considered very useful in their provision of care to this population. Most PCP use online resources and continuing medical education events to obtain information about breast cancer. It follows that current breast cancer information should be made available in those formats.

Health Care Strategies to Promote Earlier Presentation of Symptomatic Breast Cancer: Perspectives of Women and Family Physicians

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KEY WORDS
Cancer, diagnosis, qualitative, family physician


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Background: Many women with symptoms suggestive of breast cancer delay presentation to their family physician. Factors associated with delay have been well described, but data on strategies to mitigate delay are lacking.

Objectives: In a qualitative study, factors related to delay were examined and changes to the health care system that might encourage earlier presentation were identified.

Methods: Individual semi-structured interviews were conducted with women who sought care 12 weeks or more after self-detection of breast cancer symptoms ($n = 14$) and with family physicians having patients in their practice who met that criterion ($n = 10$).

Results: By examining the perspectives of these women and family physicians, we were able to develop a pattern recognition aid for the “at-risk situation for delay” in a diagnosis of breast cancer and to identify changes to the health care system that might encourage women with self-identified breast cancer symptoms to present earlier.

The “at-risk situation for delay” in presentation occurs when a woman has

- better messaging about breast awareness.
- better compliance tracking and reminders for screening mammography and periodic health exams.
- improved access to a rapid diagnostic process.
- education initiatives:
  - Improving awareness that a previous benign breast diagnosis does not ensure that future symptoms are not cancer
  - Improving the awareness of non-lump presentations of breast cancer
  - presentation of additional hopeful testimonials: “Breast cancer is not a death sentence.”
  - validation of women presenting with breast complaints.
  - improved recognition of subtle clues and indirect communication (doorknob syndrome, “Do I need a mammogram?”).

Conclusions: Family physicians are uniquely positioned to encourage women with breast cancer symptoms to present earlier. Our work emphasizes the benefit of establishing an ongoing supportive therapeutic relationship with patients and the value of regular periodic health exams and mammographic screening. Education about non-lump breast cancer symptoms and physician recognition of the “at risk situation for delay” may reduce the likelihood of women presenting late with breast cancer symptoms. More consistent messaging about breast awareness, screening mammography recommendations in women 40–49 years of age, and hopeful testimonials from women living with breast cancer is also warranted.

Establishing a Multicentre Clinical Research Network: Lessons Learned

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KEY WORDS
Clinical cancer research, research network, multicentre, network evaluation, collaboration

Methods: Mid-way through the 5-year granting period, an external review panel provided a formal midgrant evaluation. Concurrently, an internal evaluation of the network by its members was conducted using a survey. Based on feedback from those internal and external evaluations, and a review of the literature, we identified several components believed to be relevant to the development of a successful clinical cancer research network. Upon completion of the term of the grant, we reviewed those components and reflected on their broader application.

Results: The elements found to be important to our success as a clinical cancer research network were these: shared vision, formal governance policies and terms of reference, infrastructure support so that busy clinicians can use their research time most effectively, regular and effective communication, an accountability framework, a succession planning strategy to address membership changes over time, multiple strategies to engage network members on an ongoing basis, regular review of goals and timelines, and a balance between structure and creativity.

Conclusions: A program of cancer research can be complex to undertake and is most effectively implemented (and fun!) when approached as a team sport. Drawing together individuals with diverse skills can greatly enhance the strength of a research team, but typically involves inviting membership at several diverse sites. Managing a team spread across a large geographic area poses special challenges. Electronic and other means of communication greatly facilitate the establishment and nurturance of a network of individuals drawn together by common goals and values, and working in a complementary manner. The successful establishment and conduct of a multi-year, multicentre clinical cancer research network led its members to reflect on what most contributed to achieving network goals. We identified several specific factors that seem to be highly relevant in promoting success. We hope that these observations will foster further discussion on the successful design and operation of research networks.

Canadian College of Medical Geneticists Guidelines for the Indications, Analysis, and Reporting of Cancer Specimens

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KEY WORDS

Cytogenetics, cancer, hematopoietic, lymphoid, tumours