Interferon α-2b for Sentinel Node Positive Malignant Melanoma?

by Michael Noble, MD, DABIM, FRCP(c)

Malignant melanoma incidence is rising faster than any other malignancy in the U.S. Combating this difficult malignancy means optimizing care at all levels: prevention, early detection, surgical and systemic therapies. Sentinel node biopsy has step forward in the management of melanoma and is considered, by the World Health Organization, to be the standard of care for cutaneous melanoma. Sentinel node biopsy (SNBs) identifies accurately the node positive and node negative populations. It spares the potential morbidity of lymphadenectomy for the group of patients who are negative and helps the pathologists to identify involved nodes for detailed analysis. Whether or not SNBx provides a survival benefit is an important question. Early data from EORTC-MG 18952, a large European trial, indicates better survival in SNBx patients than in patients with palpable node involvement. Previous studies have shown that in general, early versus late lymphadenectomy provides survival benefit. Additionally, patients with nodal micrometastases, and immediate nodal dissection, have a significant survival benefit compared with delaying dissection until palpable disease develops (at five years, 48% versus 27% survival). Identifying sentinel nodes allows the pathologist to concentrate in great detail on involved nodes, both with very detailed histologic techniques as well as using gene probes and molecular markers to detect submicroscopic disease. There is a sense that histologic “micro-staging” of SNBx will be a predictor of prognosis. It is less clear whether the molecular staging is of value. In other malignancies, in particular colon and breast, the patient group who are node positive only on molecular testing may have a prognosis similar to node negative patients. Survival rates after surgical resection of histologically positive lymph nodes in malignant melanoma are low. In the BCCA experience of regional lymphadenectomy1, 10 year survival rates were 37% (clinical stage 1, pathologic stage 2 [CS1PS2]), 45% (CS2PS2), 26% for patients with lymphadenectomy for recurrent melanoma, and 76% for CS1PS1 patients. Survival rate differences in node positive patients were not statistically significant. CS1PS1 and CS1PS2 patients all had...
From the Editor

Welcome to the summer issue of the SON newsletter. The newsletter continues to evolve with the goal of making this a regular read for the busy practitioner. The SON was present at the BC Surgical Society spring meeting and presented the work of the Council to the general surgeons of the province. In future the goal will be to present homegrown data from various research and outcome initiatives from within BC. There are a number of energetic initiatives within the surgical tumor groups to link surgeons to a database to provide prospective data on outcomes in BC. These are exciting developments and I urge all surgeons to get involved if they have an interest in a particular tumor group. The breast and colorectal tumor groups are the most advanced but there is still a long way to go. The chairs of the tumor groups will welcome any reasoned input.

The SON sponsored a very successful melanoma conference in Kelowna and in this issue, a debate regarding the adjuvant use of Interferon is presented with Dr. Ken Wilson and Dr. Michael Noble presenting opposing views on the topic for your elucidation.

As always we are dependent on your feedback regarding the contents. Please feel free to email your comments and ideas regarding the newsletter or the SON. I look forward to hearing from you.

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Mark Your Calendars – Upcoming Conferences

Wednesday, September 17th, 2003
Optimizing Rectal Cancer Management: TME Techniques, Imaging, Adjuvant Therapy
St. Paul’s Hospital, Vancouver, BC
For more information contact Anne Finneran at 604 806-8046 or email afinneran@providencehealth.bc.ca

November 28th and 29th, 2003
Annual BCCA Partners in Cancer Care Conference
Fairmont Hotel Vancouver, Vancouver, BC
This year’s theme is Risk Reduction in Cancer/Hot Topics in Surgical Oncology. For more information go to www.bccancer.bc.ca and click on the link under Health Professionals Info. More information and a full surgical program will be sent out to all surgeons in September.

BCCA Conference Call for Posters

Abstracts are now being accepted for poster presentation. All cancer-related posters authored within the last two years are welcome.

Content
Abstracts must adequately describe the objectives and results so that the quality, originality and completeness of the work can be evaluated. Each abstract must contain: Objective, Design, Materials & Method, Results, Conclusion.

Format
1. Submit abstracts on 1 – 8½” x 11” page by email attachment as a Word 97 or Word 2000 document to nadams@bccancer.bc.ca.
2. Abstracts must be typed and single-spaced.
3. Abstract title in CAPITAL LETTERS, and followed by the name(s) of the author(s). Presenting author must be underlined.
4. Use of standard abbreviations is desirable.
5. All presentations must be in ENGLISH.
6. Accepted presenters must register for the conference.
7. An individual may present more than one abstract.
8. Presenting author must include contact information (telephone, fax and e-mail address) with abstract.
9. Accepted abstract presenters will be notified by the poster session organizers.
10. For accepted abstracts, multiple copies (approx. 30) must be available at the display site for distribution.
11. Deadline for submission: October 17, 2003
Current Management of Melanoma: An Overview

by Adam Meneghetti, MD, CCFP, MHSc

The incidence of melanoma is rising. This year in British Columbia, it is estimated that there will be over 500 new cases of melanoma and there will be over 3,000 new cases in Canada.¹ As more patients will be referred to surgeons for the diagnosis and management of this cancer, it is important for all surgeons to be aware of current treatment guidelines.

The original staging of melanoma involved the use of Clarke levels (I to V) and later, Breslow thickness of the lesion in millimeters. Current staging uses the new AJCC system:

| Stage I: Localized | T1a or b: <1 mm, non-ulcerated or ulcerated T2a: <2 mm, non-ulcerated |
| Stage II: Localized | T2b: >2 mm, ulcerated T3a or b: <4 mm, non-ulcerated or ulcerated T4a or b: >4 mm, non-ulcerated or ulcerated |
| Stage III: Regional Metastasis | N0: 1 N+ N2: 2-3 N+ N3: 4 N+ (or matted, in transit) |
| Stage IV: Distant Disease | M1: Distant skin or nodes M2: Other sites or increased LDH |

Biopsy of melanotic lesions may be incisional (punch) or excisional and will depend on the location and size of the lesion, as well as the cosmetic result desired. Excisional biopsies should take into account the possible need for further wide excision. On limbs, these are best oriented longitudinally. For in situ melanoma, a circumferential resection margin of 5 mm is recommended. For lesions less than or equal to 1.0 mm thick, a resection margin of 1 cm is preferred. For lesions that are greater than 1.0 mm thick, a 2 cm resection margin is recommended, if technically feasible. The final excision should extend down to the underlying fascia.

Basic staging includes the history and physical, as well as a chest X-Ray and a serum LDH. The estimated risk of metastasis to regional lymph nodes with T2 melanomas ranges from 20% to 25%.² Patients with T2-4 lesions and clinically negative lymph nodes, can be offered a sentinel lymph node biopsy (SLNB). Wide excision should be deferred until a consultation for SLNB has been obtained. SLNB primarily offers prognostic information, by staging the nodes more accurately. Use of both a radiopharmaceutical and blue dye for the SLNB are recommended to reduce the false negative rate.

The methods used to process the sentinel node include multiple sectioning and immunohistochemical analysis. Some centers have added PCR to this analysis. The importance of micrometastases to lymph nodes and whether adjuvant therapy should be administered as part of their treatment is still unknown. Phase III of the Sunbelt Melanoma Trial³ is a multicenter, randomized control trial that will attempt to determine the importance of micrometastases and whether interferon should be offered to patients with positive sentinel nodes as part of their therapy. Patients with positive sentinel nodes are currently offered completion node dissection for improved local control. All patients with clinically positive nodes should undergo therapeutic node dissection for local control. This may be supplemented by adjuvant radiation depending on the final pathology report.

For patients with Stage IV disease the options for therapy include single agent chemotherapy (dacarbazine or DTIC), combination chemotherapy, biological response modifiers (Interferon, Interleukin-2 etc.), vaccines, or biochemotherapy. The objective response rate to DTIC alone is approximately 10% to 20% but responses are usually short lived, ranging from 3 to 6 months.⁴ Randomized trials comparing multiple drugs to DTIC alone have not consistently demonstrated any advantage of combination therapy. Response rates for Interferon and Interleukin-2 range from 8% to 22%, although both drugs are associated with significant side effects.⁵,⁶ A meta-analysis of 20 randomized trials comparing the use of DTIC to combination chemotherapy with or without immunotherapy found no difference in overall survival, although the tumor response rate was greatest in the DTIC plus Interferon group.⁷ As of yet, there is no evidence to suggest that biochemotherapy is more effective than chemotherapy. Additional therapies for Stage IV disease may include palliative radiation or surgical resection for select patients with an isolated metastatic lesion. The latter can be associated with an increase in 5-year survival.

References


Dr. Adam Meneghetti is in his last year of residency (R6) in the UBC program of General Surgery. He is originally from Vancouver and has done all his undergraduate and graduate training at UBC.
Patients requiring thoracic surgery in British Columbia will soon receive treatment at one of four specialty centres thanks to a new provincial program spearheaded by Drs. Mike Humer and Ken Evans of the BC Chest Surgeons Association and Brian Schmidt of the Provincial Health Services Authority. “Centres for Thoracic Surgery began operating at Vancouver General Hospital and Kelowna General Hospital in December 2002 and January 2003 respectively,” stated Mr. Schmidt, “and we anticipate opening Centres in Victoria and the Fraser Valley later this year.”

The move to establish a provincial program comes as a surgeon-driven solution to improve the effectiveness and sustainability of thoracic surgery in BC. Such consolidation, the first of its kind in any jurisdiction, will enable better coordination of surgical services and enhance retention and recruitment of trained thoracic surgeons and residents. The latter will be achieved through clinical service agreements resulting in nationally competitive salaries for thoracic surgeons and better recruitment conditions.

“We will also ensure more effective use of health care dollars and better patient outcomes through ‘critical massing’ of specialized thoracic services in regional centres including knowledgeable thoracic teams of care givers and the availability of appropriate technology and support,” noted Dr. Richard Finley, Professor and Head of the UBC Division of Thoracic Surgery and Chair of the BC Surgical Oncology Network’s Thoracic Surgical Tumor Group. “The new centres will also allow the thoracic surgeons at each site to participate in research and the teaching of medical students and residents,” added Dr. Finley.

Thoracic malignancy continues to be the major component of thoracic surgery practice. In British Columbia, lung cancer is now the most common cause of death in both men and women. By the year 2006, The British Columbia Cancer Registry projects there will be approximately 3,000 new lung cancers per year in the province. The incidence of adenocarcinoma of the esophagus is increasing at a rate of 4% per year in British Columbia. By the year 2006, the BC Cancer Registry estimates there will be 228 new cases of esophageal cancer per year. Patients with these malignancies will be managed by multi-disciplinary teams from each of these centres using modern evidence-based thoracic surgery techniques. Lung transplantation surgery will occur at the Vancouver General Hospital. Outreach clinics are a key component of the program to ensure access to surgical consultation and care throughout the province.

“The Ministry of Health and all the Health Authorities played a vital role in developing this program,” noted Mr. Schmidt. “Ideally, we will create a model to plan other provincially coordinated medical or surgical services in the future.”

For more details, contact Mr. Brian Schmidt at bschmidt@phaa.ca.

Thoracic Perspective: Dr. Michael Humer

Dr. Michael Humer is one of BC’s thoracic surgeons who initiated the newly established Provincial Program for Thoracic Surgical Care. Previously a surgeon at Kamloops’ Royal Inland Hospital, he recently moved his practice and home to Kelowna in support of the provincial program’s objectives. His insights on the advantages and opportunities follow:

What does a provincial program do to increase the availability of thoracic expertise in BC?

Thoracic surgery is the smallest adult surgical section in the province. Until now, we experienced a significant net loss of thoracic surgeons due to retirement and relocation to other provinces. The latter resulted from the fact that most thoracic practices here consisted of one or two surgeons with excessive on-call duties, an unsustainable workload and lower remuneration relative to their peers. I am the only new thoracic surgeon to come to BC since 1996.

The Provincial Program will ensure three thoracic surgeons are available at each Centre enabling continuity of care in terms of on-call requirements and sufficient collegial support for CME opportunities and time off. With a catchment area of one million people per Centre, the Program aligns us much closer with the guidelines of the Canadian Association of Thoracic Surgery: one surgeon per 300,000 people. We are also recruiting a fourth surgeon for the Vancouver Centre whose expertise is transplantation.

How will service consolidation effect patients in outlying areas?

An outreach program is integral to ensure everyone receives the right treatment in a timely manner. The massive distances between Centres will be lessened through four outreach clinics located in Prince George, Cranbrook, Trail and Kamloops. Patients living far from a major Centre will receive most of their consultation and care through one of these clinics and usually require only one visit to a Centre for surgery. Eventually, we plan to use telemedicine and distant patient technologies extensively.

What is the initial reaction to the Program?

All of our discussions with government and the Health Authorities have been tremendously supportive. We are all working to improve accessibility and standards of care and delivery. The process began in 2001 and we are now working to implement the second half of the proposal.

Dr. Michael Humer is a thoracic surgeon with the Interior Health Authority’s new Centre for Thoracic Surgical Care at Kelowna General Hospital. He played a key role in the development of a consolidated thoracic surgical care program for BC. Contact Dr. Michael Humer at mhumer@shaw.ca.
CME

- A successful workshop on the Current Management of Melanoma was held in Kelowna on May 23rd, 2003. Attended by over 20 physicians, presentations included a pro and con discussion of the role of Interferon in the Adjuvant Treatment of Melanoma. This workshop will be presented in other regions in the province.
- Work continues on the Medline Internet Tutorial Course. We hope to have this course accredited and fully functional by the year’s end.
- On November 29th the Surgical Oncology Network will once again host a one-day education conference in connection with the BC Cancer Agency’s Annual Cancer Care conference. This year’s theme for the surgical day will be Hot Topics in Surgical Oncology.

Surgical Tumour Site Groups

- The Colorectal Surgical Tumour Group will be holding another TME workshop on September 17th, 2003.
- The Breast Surgical Tumour Group has put together a working group to develop a provincial guideline for Sentinel Node Mapping for breast cancer.

Clinical Practice

- The inaugural meeting of the clinical practice committee was held on June 25th. Two initial goals of the committee will be to develop a template for clinical practice guidelines and to identify the necessary information that needs to be collected to conduct a resource inventory for surgical oncology.

Book Review

Title: Radioguided Surgery

Editors: Whitman ED and Reintgen D

Publisher: Vademecum, Landes Bioscience
Austin, Texas, USA 1999
www.landesbioscience.com

Reviewer: Dr. R. Cheifetz,
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This handbook is a compilation of chapters written by well-known surgical oncologists, radiologists and pathologists from major cancer care centers in the United States. It begins by addressing the general issues surrounding the organizational development, radiation safety issues and physician training for radioguided surgery programs. This is followed by a detailed discussion on the clinical aspects of sentinel lymph node techniques, as they apply to both melanoma and breast cancer. It also addresses the nuclear medicine methods of lymphoscintigraphy and the procedures for pathologic analysis of sentinel nodes. In addition, chapters are devoted to the application of radioguided techniques in parathyroid surgery, other skin cancers, vulvar carcinoma and bone lesions.

This excellent handbook is a must-read for any surgeon or group interested in establishing a sentinel node biopsy program at their institution. It is also of value for those who already do sentinel lymph node biopsy and other radioguided techniques to ensure that they are providing a high quality program. The text is well written, easy to read and very comprehensive.

Scott Ellerbeck from Schering Canada Inc. has very generously donated 5 copies of this book to the Surgical Oncology Network. If you would like a copy please phone or email the Network at 604-877-6000 ext. 3269 or son@bccancer.bc.ca. We will hold a lottery if more than 5 surgeons express an interest in receiving the book.
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populations. In melanoma there is some evidence that positive molecular markers worsen prognosis.3

While techniques such as SNBx will help to identify high risk cases, this is of little benefit to the patient unless there is an effective therapeutic intervention. Finding effective adjuvant therapy in melanoma, a malignancy relatively refractory to systemic therapy, has been difficult. The most promising, and most intensely scrutinized trials, are those of the Eastern Cooperative Oncology Group (ECOG, Trial E1684, 1690, and 1694). These all used high dose Interferon as adjuvant treatment. Numerous trials using lower doses of Interferon have been negative. The essence of the ECOG trials follows:

Trial E1684, which compared Interferon alpha-2b to no treatment in high risk, lymphadenectomized patients, showed a significant survival benefit for high dose therapy with Interferon, and led to the licensing of Interferon alpha-2b for this indication in North America. At 12.6 years after completion of the trial, the overall survival (OS) difference has diminished to the point where it is no longer statistically significant. However, the disease free survival (DFS) remains significantly better (37% versus 25%). In this old trial, patients are beginning to die from causes other than melanoma.6,7 Increasing a patient’s odds of being alive every year for the next 12.6 years is considered significant by many clinicians.

The subsequent ECOG trial (E1690) is difficult to interpret because of a cross-over study design which permitted control patients who relapsed in lymph nodes to then receive therapy with Interferon. To some extent this was a trial of early versus late adjuvant Interferon therapy. While there was no overall survival difference, again there is a disease free survival difference, which remains significant for the Interferon alpha-2b treated patients (44% versus 35%).8

A third trial, E1694, also showed a significant benefit in both OS and DFS for high dose Interferon (OS: 78% vs 73%, DFS: 62% vs 49%). The difference was significant enough that the trial was closed early because of the degree of difference between the arms. It was felt unethical not to offer all patients Interferon therapy. The survival differences continue to be significant.9

A European trial (EORTC-MG18952) closed in 2001 with over 1400 patients using an intermediate dose Interferon regimen, which is likely suboptimal dosing. Despite this, early analysis again shows significant benefit in metastasis free survival for the Interferon arms (p=0.145).1

Ongoing trials, particularly the Sunbelt Melanoma Trial, include patients in intermediate risk groups. The role of sentinel node biopsy microstaging and molecular markers in predicting patient benefit are being assessed. All histologically node positive patients, except ½ of those with thin primaries and solitary nodes (an identified favorable prognostic group) receive adjuvant Interferon alpha-2b as standard therapy.

The ultimate question for the clinician is how to translate existing data into patient management decisions. Treatment of systemic relapse in melanoma is rarely effective, and every effort should be made to prevent recurrence. High dose Interferon alpha-2b is a challenging treatment - a month of I.V. Interferon, five days out of seven and then eleven months of subcutaneous treatment three times a week. Elderly or medically unwell patients are not good candidates. A full course of adjuvant Interferon is expensive (about $26,000 Canadian a year). In British Columbia it is not a Pharmacare benefit and is a benefit from BCCA only in some patients who have bulky, grossly palpable nodes. Most extended health plans will cover high dose adjuvant Interferon alpha-2b. All provinces in Canada outside of B.C. will pay for high dose Interferon alpha-2b adjuvant therapy. On balance, the current evidence for adjuvant Interferon as standard therapy is compelling - in my practice, all suitable patients with high-risk10 melanoma are offered adjuvant treatment with high dose Interferon alpha-2b.

References


undergo lymphadenectomy. Whether SNBx positive patients sustain a superior survival than those who do not have the procedure is the subject of The Multicenter Selective Lymphadenectomy Trial\(^1\).

Many adjuvant therapies have been investigated in node positive melanoma. When the Eastern Co-operative Oncology Group (ECOG) presented results of Trial E1684 showing an overall survival (OS) benefit with high dose Interferon alfa-2b\(^4\), there was a sense of oncologic relief that an effective agent had at last been identified.\(^4\) This finding led to approval in the USA and Canada of high dose Interferon alfa-2b as adjuvant therapy for high risk melanoma. However, in further follow up (median 12.6 years), the benefit in OS was no longer statistically significant.\(^5\) Furthermore, E1684 was not stratified prospectively for number of positive nodes, a factor now included in the new AJCC melanoma staging system.\(^6\)

ECOG have reported 2 subsequent trials (E1690 and E1694) in high risk melanoma.\(^7,8\) E1690 was intended to be a confirmatory trial evaluating also a lower dose of Interferon alfa-2b. Unfortunately, E1690 showed absolutely no survival benefit from either low dose or high dose Interferon alfa-2b. In the group of patients with one lymph node positive, there was not even a suggestion of improvement in relapse-free survival (RFS) with high dose Interferon alfa-2b. In E1694, at median follow-up of 16 months, OS was 5% better for patients receiving Interferon alfa-2b (OS 78% vs 73%). Although E1694 results are positive at this point, the loss of significance of OS benefit with mature follow-up in trial E1684 suggests caution in interpretation of E1694 results.\(^9,10\) It should also be noted that none of the ECOG studies were powered to detect gains in different patient subgroups for RFS or OS. Furthermore, none of the trials reported results specifically in SNBx positive patients.

Although each of the ECOG trials showed consistent benefits in prolongation of disease free survival (DFS), there has been no consistency in subgroup benefits. In E1684, the largest treatment effect was in CS2PS2 patients, in E1690 those with 2–3 lymph nodes involved, and in E1694, those with T4 primary melanoma without nodal involvement.

Individual adjuvant Interferon alfa-2b trials often lack power to detect potentially significant OS benefits. For example, in order to have 80% power to detect an absolute increase of 10% in OS with \(p = 0.05\), 800 patients are required. Hence, meta-analyses have been performed to strengthen the power to detect small changes in RFS and OS.

ECOG conducted a pooled analysis of 4 high dose Interferon alfa-2b trials and concluded that OS was superior with Interferon alfa-2b.\(^11\) Trial heterogeneity and short follow-up of the 2 most influential trials are problematic with this analysis.\(^10\) Meta-analysis of high dose interferon trials with observation controls\(^12\) showed no significant OS benefit (\(p = 0.1\)). A systematic review of phase III trials comparing regimens with or without adjuvant interferon therapy (low, intermediate or high dose schedules) identified 9 trials of which 8 were published.\(^13\) Since there was wide clinical heterogeneity between trials, meta-analysis was considered inappropriate. These investigators could not confirm improvements in RFS in E1690 patients or in OS in E1684 patients.

Controversy over the benefit of adjuvant high dose Interferon alfa-2b continues, with European opinion solidly concluding that it is still “investigational” across all categories of high risk melanoma patients.\(^9\) In USA and Canada, Interferon alfa-2b remains approved for clinical use in these situations, but physician enthusiasm and utilisation of adjuvant Interferon alfa-2b is tempered by the established toxicity and quality of life changes, cost and effectiveness, especially when the latter is debatable.

There are no completed clinical trials addressing the role of adjuvant Interferon alfa-2b in SNBx positive patients. The

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Dr. Wilson started GP rounds with his dad at age 3 and later qualified Bachelor of Medicine in Edinburgh, 1970 with subsequent Doctorate in the Faculty of Medicine (MD, 1974). He trained in Internal Medicine in Edinburgh, and emigrated to Canada and the Saskatchewan Cancer Foundation in 1977 where he began his career in medical oncology. He became one of the first 2 board certified medical oncologists (ABIM, Med Onc) in the province (1979). He moved to the Victoria Cancer Clinic in 1980 where he was the only full time specialist in medical oncology for 8 years. Dr. Wilson has broad oncology interests and has publications in all the major tumor groups. He has been closely linked with the NCIC Myeloma and Melanoma Groups, and authored the report of the NCIC MY3 Trial. Along with Dr. Jan Lim, he pioneered radical chemoradiotherapy for esophageal cancer in the BCCA. Dr Wilson’s main non-medical interest is music, highland bagpipe being the instrument of choice. He is married with 3 “children”, one a graduate of U Vic, and 2 others in the pipeline at U Vic and U of Calgary.
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present ME10 Trial of the NCIC Clinical Trials’ Group and the Sunbelt Melanoma Trial include SNBs positive patients with randomizations to 1 month and 12 months of high dose Interferon alpha-2b respectively. The control group in each of these trials receives surgery alone. Hence surgery alone is the standard of care in SNBx positive melanoma patients.

References


