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The Swedish Melanoma Study Group - a Brief History

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INTRODUCTION

The Swedish Melanoma Study Group (SMSG) is a collaborative group of Swedish physicians and scientists working in the field of melanoma. The aim of the SMSG is to ensure a high quality of melanoma health-care in Sweden, including prevention, diagnostic activities, treatment and care of melanoma patients. This is achieved by exchange of information by education and by performing research and development activities including the conduct of clinical trials and the establishment of a Swedish National Melanoma Care Program and a National Melanoma Quality Registry.
The SMSG was formed in 1977 by an initiative of Dr. Ulrik Ringborg, an Oncologist at the Karolinska Institutet in Stockholm, and Drs. Carl-Magnus Rudenstam and Lars Olof Hafstrˆm, both surgeons at the University of Gothenburg (U Ringborg, personal communication). The SMSG has developed to a multidisciplinary group with members form all six health care regions in Sweden. The SMSG has general member meetings at least two times yearly, as well as special working meetings of sub-groups. The activities of the SMSG are supported by a grant from the Swedish Cancer Society.

ACTIVITIES OF THE SMSG

Prevention

In 2003 1,889 new cases of invasive cutaneous melanoma was registered in the Swedish National Cancer Registry (1). Cutaneous melanoma is one of the malignant tumors with the most rapid rate of increase in incidence in Sweden. To address this increasing health care problem the SMSG has focused several activities on prevention. Together with other organizations, the SMSG has supported information and prevention campaigns aimed at the general population, including "open house" activities with free examination of pigmented skin lesions.
In 1987, a program was initiated by the Swedish Melanoma Study Group with the aim to identify and provide a preventive program to Swedish kindreds with hereditary predisposition for cutaneous melanoma and dysplastic nevus syndrome. The specific aims of this ongoing program, which is carried out in 12 specialized outpatient clinics, are to identify all such kindreds, to provide counseling and primary and secondary prevention to family members, and to collect family data in a central data base for scientific purposes. The program is carried out in 12 specialized outpatient clinics representing all parts of Sweden, except the Southern Health Care Region, corresponding to a population of 7.3 million inhabitants and representing 82% of the Swedish population. A standardized national protocol is used for data collection and data on all individuals are registered in a central database at the Department of Oncology, Radiumhemmet, Karolinska University Hospital, Stockholm. The regional DNS teams meet yearly to coordinate the process at the national level. At present over 350 kindreds with hereditary melanoma have been identified and members are followed at the participating specialized outpatient clinics.
In conjunction with this program, molecular genetic studies have been performed and an ancient CDKN2A germline founder mutation has been detected in a proportion of these kindreds, as well as in kindreds from Southern Sweden examined by a research group in Lund (2-3). The groups in Lund and Stockholm are active participants in an international collaboration on melanoma genetics organized by the Melanoma Genetics Consortium, Genomel.

CLINICAL TRIALS

Surgery

The SMSG has organized large prospective trials in melanoma which have had impact on the management of melanoma in Sweden and internationally. From1982 to 1991, a large Swedish randomized phase III trial of patients with melanoma with a tumor thickness according to Breslow of 0.8 - 2.0 mm was performed (4). A total of 989 patients were randomized to one of two surgical treatment groups with total excision margins of either 2 or 5 cm, respectively. The aim was to investigate whether an excision margin of 2 cm is sufficient. The long term follow up results of this trial showed no significant difference with respect to recurrence-free or overall survival between the groups (5). As a result of the trial, an excision margin of 2 cm is recommended for patients with T2 tumors (thickness 1.1-2.0 mm) in Sweden.
After the above study was concluded, the question remained whether excision margins of more than 2 cm was required for primary melanomas with a tumor thickness above 2.0 mm. To address this question the SMSG has participated in performing a Scandinavian - Baltic trial of resection margins, with study centers in Denmark, Estonia, Norway, and Sweden. The trial randomized patients with primary cutaneous melanomas with a tumor thickness above 2.0 mm (T3-T4 tumors) to be treated with either a total excision margin of 2 cm or a margin of at least 4 cm. Between 1992 and 2004 a total of 936 patients were randomized in this study and the results are now being analyzed.
The issue of elective lymph node dissection has been debated in melanoma. In particular, data regarding the possible value of elective lymph node dissection in head-neck melanomas have been lacking. Therefore, the SMSG performed a retrospective evaluation of patients with primary melanomas of the head and neck (6). This study showed no survival benefit for elective lymph node dissection in head-neck melanomas and this procedure has thus been abandoned. In addition to the study on elective lymph node, dissection the SMSG has also published a report on treatment results and prognostic factors in Swedish patients with primary head-neck melanoma (7)
The SMSG has organized a prospective program to implement and evaluate the sentinel lymph node biopsy (SLNB) technique in patients with primary melanoma. Initially, the SMSG recommended SLNB in melanomas with a tumor thickness above 1.5 mm. The SLNB method has now been established in most major centers in Sweden and the recommendation for SLNB has been modified to include all patients with trunk or extremity melanomas with a tumor thickness above 1.0 mm, to adopt internationally accepted guidelines.

Adjuvant therapy

In a randomized prospective trial performed by the SMSG of adjuvant hyper-

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thermic perfusion with melphalan after surgery for recurrent malignant melanoma of the extremities, a significantly improved recurrence-free survival was demonstrated, without a significant impact on overall survival (8).
Between 1996 and 2004, the SMSG participated in a large Nordic randomized phase III trial of adjuvant interferon therapy in high-risk melanoma. Patients with primary melanoma with a tumor thickness above 4.0 mm (T4 tumors) and/or with regional lymph node metastases were randomized to one of three study arms. Patients in arm A were followed without therapy while patients in arms B and C both received interferon alfa-2b in intermediate doses ($10x10^6$ IU injected S.C. 5 times per week during a 4 week induction phase followed by maintenance therapy with the same dose administered 3 times per week). Patients in arm B received maintenance therapy for 12 months and those in arm C for 24 months. The trial was closed for recruitment in July 2004 after randomization of 855 patients. Analysis of the results is planned no later than 2007.

Therapy for advanced disease

The SMSG has performed a couple of randomized trials of chemotherapy in inoperable metastatic melanoma. In an initial randomized controlled study, 119 patients with disseminated malignant melanoma were randomized to receive treatment with dacarbazine (DTIC) alone or in combination with vindesine (9). The study was designed to reveal an additive response rate when the drugs were combined. In the DTIC single agent therapy arm, the overall response rate was 18% compared to 25% in the DTIC-vindesine arm. The difference was not statistically significant. There was also a statistically non-significant trend towards more prolonged response duration in patients treated with the combination of DTIC-vindesine compared to DTIC alone.
This initial study was followed by a randomized multicentre phase III study performed in Sweden and Norway addressing the effect of adding cisplatin to DTIC-vindesine combination therapy (10). In this trial, 326 patients were randomized to receive treatment with the combination of DTIC and vindesine with or without the addition of cisplatin. The overall response rate in the DTIC-vindesine arm was 21%, compared to 31% in the DTIC-vindesine- cisplatin arm. This difference was not statistically significant. The median time to progression was significantly longer in patients treated with DTIC-vindesine-cisplatin (4.2 versus 2.2 months, $P=0.007$). There was, however, no statistically significant difference in overall survival between the treatment arms. Increased toxicity, particularly leucopenia, alopecia and nausea/vomiting, was observed in the treatment arm containing cisplatin. Thus, adding cisplatin to DTIC-vindesine did not improve overall survival but significantly increased toxicity.
The conclusion of these trials is that single agent therapy with DTIC, or the more recent drug temozolomide, should remain the recommended therapy, outside clinical trials, for patients with advanced disseminated melanoma.

National Melanoma Care Program and Quality Registry

In order to promote a uniform high quality of melanoma care and participation in clinical studies, the SMSG has developed a Swedish National Melanoma Care Program. This National Care program consists of a document that is regularly updated and contains a summary of the State of the Art regarding melanoma, as well as guidelines for prevention, diagnosis, treatment, and follow-up of melanoma patients.
The Care Program is linked to a National Melanoma Quality Registry. All new cases of cutaneous melanoma are uniformly registered through the Regional Melanoma Registries in each of the six health care regions of Sweden. Data on patient characteristics, clinical and histopathological information regarding the melanoma tumor including disease staging according to the present TNM classification, as well as data on treatment and follow-up are collected. The data are annually reported to and compiled in a national database.
Recently a report from the National Melanoma Quality Registry on a prospective population based study of survival and prognostic factors of invasive cutaneous malignant melanoma in Sweden 1990-1999 was published (11). In total, 12,533 patients, corresponding 97% of all registered melanomas in Sweden during this period, were included and described. A multivariate analysis showed that factors with a negative effect on survival included Clark level of invasion, Breslow thickness, presence of ulceration, older patient age, trunk location, large tumor diameter, nodular histogenetic type, and male gender. Interestingly, the analysis showed that during the study period from 1990 to 1999, the 5-year survival of patients with malignant melanoma in Sweden was better compared with the previously reported rates in published, population-based studies from Sweden, probably as a result of improved secondary prevention due to better knowledge and awareness by both patients and the medical profession. The more favorable prognostic factors and a change in primary melanoma site found in younger patients, compared with earlier reports, may reflect changes in clothing as well as tanning habits. The authors concluded that further improvements could be achieved with better access to health care and with the use of early melanoma detection campaigns. Further analysis of this patient material as well as of patients diagnosed after 1999 is ongoing.

FUTURE DEVELOPMENTS

The SMSG will continue to promote excellence of care and research in the melanoma field in Sweden, by acting as a coordinating group. An important tool in this respect is the National Melanoma Care Program and the National Melanoma Registry. Several of the achievements of the SMSG have involved Nordic/Baltic collaborations. In order to promote future joint international projects and studies, the SMSG will seek to develop further international collaborations with other organizations such as the Nordic Melanoma Groups, the EORTC, and Genomel.

CONCLUSION

The story of the SMSG shows that a national cooperative group can be of considerable importance for the coordination of clinical activities and research. Moreover, by coordinating and performing national and international multicentre trials it is possible to obtain results with a significant impact on the management of patients with melanoma.

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