Award Lectures

FECS Pezcoller Award Lecture

444

A 30-year trek through the arcanes of clinical research

Jean-Claude Horiot. *Centre G.-F. Leclerc, Dyon, France*

Thanks to the education received from Jean Papillon and Gilbert H. Fletcher, I was prepared to undertake research in a variety of fields of oncology. However, I would not have achieved very much alone and my chance was to be involved very early on in cooperative research.

I will just point out a few representative landmarks of this path.

- The demonstration of the effectiveness of Fluoride topical application to prevent dental caries in irradiated patients: this highly controversial hypothesis soon became the state of art and contributed to an improved quality of life for thousands of patients [1].
- The optimal management of cervix cancer with radiotherapy alone (external radiotherapy followed by intracavitary brachytherapy): Gilbert H. Fletcher and Felix Rutledge made the demonstration that surgery was no longer necessary and that improved results could be obtained in moderately and advanced disease. From there on, we developed a customized treatment planning which resulted in an improved loco-regional control and a drastically decreased incidence of severe complications [2]. The ICRU 38 recommendations were withdrawn from this work made in cooperation with the GEC (European Group of Curietherapy).
- The year 1975 witnessed the creation of the EORTC Radiotherapy group and the start of the still on-going venture which allowed European cooperative research in Radiotherapy to stand among the best in the world. Major pivotal trials were undertaken in hyperfractionated and accelerated radiotherapy which demonstrated the clinical relevance of biological hypotheses [3,4]. Other progress was achieved in the management of head and neck, rectum, anal, breast and prostatic cancers. Not only radiation oncology techniques and strategies were improved but also major progress could be achieved in multidisciplinary strategies, surgery and medical by extended cooperation with organ oriented groups (breast, prostate, head & neck, brain, gastro-intestinal, lung, etc.) In 1982, a systematic quality assurance programme was launched by the EORTC Radiotherapy group [5,6]. Welcomed with skepticism, this initiative became a model in a few years for quality assurance in the physics of radiation beams and soon was extended to patients and clinical research data management. This pioneer work was extended to all other disciplines in EORTC and later passed onto standard practice. This led me to an even closer contact with other disciplines involved in clinical research and ultimately to the Presidency of EORTC. Together with 300 hospitals and more than 2000 enthusiastic scientific partners, we must meet another challenge resulting from the explosion of our basic knowledge on cancer growth, sensitivity and resistance of tumor and normal tissues to therapies.This exciting period is the dawn of new strategies and novel therapies for the benefit of our cancer patients.

[1] Horiot J.C., Schraub S., Bone M.C., Bain Y., Ramadier J., Chaplain G., Nabid A., Thevenot B., Bransfield D.: Dental preservation in patients irradiated for head and neck tumors: a 10-year experience with topical fluoride and a randomized trial between two fluoridation methods. Radiotherapy and Oncology, 1, 77–82, 1983.

[2] Horiot J.C., Pigneux J., Pourquier H., Schraub S., Achille E., Keiling R., Combes P., Rozan R., Vrousos C., Daly N.: Radiotherapy alone in carcinoma of the intact uterine cervix according to G.H. Fletcher guidelines: a French cooperative study of 1383 cases. Int. J. Radiation Oncology Biol. Phys. 14, 605–611, 1988.

[3] Horiot J.C., Le Fur R., Nguyen T., Chenal C., Schraub S., Alfonsi S., Gardani G., van den Bogaert W., Danczak S., Bolla M., van Glabbeke M., de Pauw M.: Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiotherapy and Oncology, 25, 231–241, 1992.

[4] Horiot J.C., Bontemps P., van den Bogaert W., Le Fur R., van den Weijngaert D., Bolla M., Bernier J., Lusinchi A., Stuschke M., Lopez-Torrecilla J., Begg A.C., Pierart M., Collette L.: Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiotherapy and Oncology, 44, 111–121, 1997.

[5] Horiot J.C., van der Schueren E., Johansson K.A., Bernier J., Bartelink H.: The programme of quality assurance of the EORTC radiotherapy group. A historical overview. Radiotherapy and Oncology, 29, 81–84, 1993.

[6] Horiot J.C., Bernier J., Johansson K.A., van der Schueren E., Bartelink H.: Minimum requirements for quality assurance in radiotherapy. Radiotherapy and Oncology, 29, 103–104, 1993.

EACR Award Lecture

445

The genetic profile of marginal zone B-cell lymphoma

J. Dierlamm[1], L. Wlodarska[2], M. Baens[2], M. Stefanova[1], K. Hinz[1], M. Stul[2], L. Michaux[2], G. Verhoef[3], J. Thomas[4], D.K. Hossfeld[1], A. Hagemeijer[2], C. De Wolf-Peeters[5], P. Marynen[2], H. Van den Berghe[2].
[1]Dep. of Hematology and Oncology, University of Hamburg, Germany; [2]Center for Human Genetics; [3]Dep. of Hematology; [4]Oncology; [5]Pathology, University of Leuven, Belgium

Marginal zone B-cell lymphoma (MZBCL) including extranodal MALT lymphoma, nodal monocytoid B-cell lymphoma, and splenic marginal zone B-cell lymphoma represents a distinct subtype of B-cell non Hodgkin's lymphoma (NHL), which has been recently recognized and classified as a disease entity. Despite the well defined clinical and pathologic characteristics of these neoplasms, the genetic mechanisms underlying their genesis and disease progression are poorly understood.

From 561 cases of B-cell NHL cytogenetically analyzed at the Center for Human Genetics of the University of Leuven, Belgium, between 1985 and 1997, 51 cases (9%) were classified as MZBCL according to the REAL classification. Thirty-three of these cases (64.7%) showed an abnormal karyotype. The main recurrent cytogenetic abnormalities detected were numerical changes of chromosome 3 (21 cases) and chromosome 18 (10 cases), the t(11;18)(q21;q21) (3 cases), and structural rearrangements with breakpoints in 1q21 (11 cases) and 1p34 (8 cases). All recurrent abnormalities and especially anomalies of chromosome 3 and the t(11;18) were found more frequently in MZBCL than in other subtypes of B-NHL.

In order to delineate the commonly overrepresented regions, comparative genomic hybridization (CGH) was performed in all cases with available DNA. Twenty of the 25 cases analyzed (80%) showed gains or losses of genetic material. In extranodal, nodal, and splenic MZBCL, material of chromosomes 3 (52% of cases), 18 (32%), X (24%), and 1q (16%) was most frequently gained, whereas losses predominantly involved chromosomes 17 (16%) and 9 (12%). Relevant subregions could be narrowed to 3q21-23, 3q25-29, 18q21-23, 1q25-31, 17p, and 9p13.

Gene rearrangement studies were performed in 32 cases of MZBCL. Three cases revealed a rearrangement of the *BCL6* proto-oncogene, whereas non of the cases showed rearrangements of the *BCL1*, *BCL2*, *BCL3*, and *CMYC* genes.

Finally the breakpoint regions of the t(11;18), the most frequent structural chromosomal abnormality in extranodal MALT lymphomas described so far, were further analyzed by fluorescence in situ hybridization (FISH) and molecular techniques. In both cases studied, the breakpoint on chromosome 11q could be mapped at 105 cM within the non-chimeric YACs 921F3 and 906C5. The breakpoint on chromosome 18 was found to be contained in YACs 949B6 and 817C6 at 81 cM. Subsequently, FISH experiments with PAC clones isolated for STSs D18S887, D18S1055, and D18S1129 contained in YAC 949B6 were performed. Starting from these PACs a walking strategy was applied and two PAC clone spanning the chromosome 18 breakpoint were identified, The breakpoints were further narrowed down by FISH analysis with *Bam*HI fragments subcloned from these PACs. Based on these data, cloning and characterization of the involved genes was performed. The *API2* gene, encoding an inhibitor of apoptosis also known as *c-IAP2*, *HIAP1*, and *MIHC*, and a novel gene on 18q21 characterized