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Motivating medical students to learn basic science concepts using chronic myeloid leukemia as an integration theme

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ABSTRACT

Objective: To report on the use of chronic myeloid leukemia as a theme of basic clinical integration for first year medical students to motivate and enable in-depth understanding of the basic sciences of the future physician.

Methods: During the past thirteen years we have reviewed and updated the curriculum of the medical school of the Universidade Estadual de Campinas. The main objective of the new curriculum is to teach the students how to learn to learn. Since then, a case of chronic myeloid leukemia has been introduced to first year medical students and discussed in horizontal integration with all themes taught during a molecular and cell biology course. Cell structure and components, protein, chromosomes, gene organization, proliferation, cell cycle, apoptosis, signaling and so on are all themes approached during this course. At the end of every topic approached, the students prepare in advance the corresponding topic of clinical cases chosen randomly during the class, which are then presented by them. During the final class, a paper regarding mutations in the *abl* gene that cause resistance to tyrosine kinase inhibitors is discussed. After each class, three tests are solved in an interactive evaluation.

Results: The course has been successful since its beginning, 13 years ago. Great motivation of those who participated in the course was observed. There were less than 20% absences in the classes. At least three (and as many as nine) students every year were interested in starting research training in the field of hematology. At the end of each class, an interactive evaluation was performed and more than 70% of the answers were correct in each evaluation. Moreover, for the final evaluation, the students summarized, in a written report, the molecular and therapeutic basis of chronic myeloid leukemia, with scores ranging from 0 to 10. Considering all 13 years, a median of 78% of the class scored above 5 (min 74%–max 85%), and a median of 67% scored above 7.

Conclusion: Chronic myeloid leukemia is an excellent example of a disease that can be used for clinical basic integration as this disorder involves well known protein, cytogenetic and cell function abnormalities, has well-defined diagnostic strategies and a target oriented therapy.

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Introduction

The Faculty of Medical Sciences of the Universidade Estadual de Campinas (UNICAMP) is considered one of the best medical schools in Brazil and in Latin America. Located in São Paulo state, in Campinas, a city of one million inhabitants and center of a technological area comparable to the Silicon Valley in California, the school enrolls 110 students from at least 10 000 candidates every year from all over the country. Thus the selection process is difficult; the exams are very rigorous, and consist of approximately one week of evaluations of chemistry, physics, biology, maths, Portuguese, literature, history, geography and English.

The undergraduate medical course is nominally six years long with the first and second years being pre-clinical and years five and six are trainee intern years.

Since the creation of the medical school 45 years ago, the first year curriculum comprises biochemistry, histology, embryology and anatomy. The courses are based on lectures, laboratory classes and examinations. During the past thirteen years we have reviewed and updated the curriculum to revitalize the course. The main objective of the new curriculum was to teach the students how to learn to learn. Horizontal and vertical integration are one focus of the new curriculum as is the integration of basic and clinical courses.

In the new curriculum, the module 'The Cell' is introduced during the first eight weeks of the course. The module is given in 168 h with 75% in class studies under teacher guidance and laboratory activities, including bioinformatics, and less than 25% reserved for lectures. We would like to report the strategy used to apply the module 'The Cell' in order to maintain the principles of the new curriculum and motivate students.

The objective of this paper is to report on the use of chronic myeloid leukemia as a theme of basic clinical integration for first year medical students to motivate and enable in-depth understanding of the basic sciences of the future physician.

Method

Chronic myeloid leukemia is a disease of the hematopoietic stem cells, which acquire a reciprocal translocation between chromosomes 9 and 22 (Philadelphia chromosome). This translocation leads to a juxtaposition of the BCR gene to the ABL gene. The ABL gene is a proto-oncogene. This juxtaposition determines the activation of ABL, a tyrosine kinase involved in the intracellular signaling which culminates in increased proliferation and reduced apoptosis of the abnormal clone.[1,2]

(1) On the first day of this module, 1 h is reserved for the students to interview a patient, cured of chronic myeloid leukemia after being submitted to bone marrow transplantation.

The students have an opportunity to hear the patient, personal and family information, the complaints which culminated in going to the doctor, and the patient's feelings regarding the diagnosis and the evolution of the disorder before and after the bone marrow transplantation.

A PowerPoint presentation is then shown summarizing the epidemiology, clinical characteristics, etiologic factors of this disease and finally, a blood smear of the patient at diagnosis and of a normal person is shown and the significant differences in the numbers of white cells and platelets is discussed. This increased amount of cells is then correlated with spleen growth which the patients had mentioned as the initial symptom, during the interview.

Then, the students are given the address of the page containing the clinical case on the Internet so that they can prepare themselves for the next classes. The Internet page includes descriptions of techniques emphasizing recently acquired basic knowledge, and videos showing the separation of proteins, Western blot test, chromosome analysis by standard karyotyping and *in situ* fluorescence hybridization (FISH), polymerase chain reaction (PCR), RNA quantification by reverse transcription PCR (RT-PCR), stem cell separation and growth, and colony formation.

At the end of each basic theme, the clinical case is presented by randomly chosen students coordinated by the teacher as follows.

(2) During the presentation of the protein theme, the students discuss the basis of the western blot technique that identified an abnormal band in the patient. A picture of the Western blot results is used as an example. Only the abnormal band, present in the patient and absent in the control, is shown.

But why does the patient present this abnormal band? The answer to that question arises during the course.

The Western blot technique is also described and students watch a video showing the procedure used to make polyacrylamide gel, the application of the sample in the gel, the migration of the proteins in the gel, the verification of these proteins using Coomassie blue stain, the transference of these proteins to nitrocellulose membrane and the revelation of these proteins using a specific antibody and a secondary antibody. Both, the video (approximately 15 min long) and a brief description of the technique are available on the internet.

(3) During the classes concerning chromosomes, gene organization and transcription, the students discuss the cytogenetics of patients with the Philadelphia chromosome. The traditional cytogenetics and FISH of the patient, as well as the procedure to perform these techniques are available in the Internet site.

At this point we discuss the relationship between the abnormal band (previously showed) and this translocation. The students discuss the genes that are involved in the translocation and the relationship between these genes and the abnormal protein.

The implication of this translocation at the RNA level and the usefulness of this knowledge in the diagnosis of the translocation are also studied. RT-PCR, used to demonstrate the BCR-ABL transcript, and the importance of RT-PCR to follow up patients after bone marrow transplantation are discussed. RT-PCR products, before and after bone marrow transplantation, are shown. Finally, students are able to associate the abnormal protein to the cytogenetics and RT-PCR.

(4) During the presentation of the topic on signal transduction and the tyrosine kinase pathways, students discuss the

role of ABL in signal transduction, the BCR-ABL hyperphosphorylation and its involvement in the signaling pathways, leading to an abnormal proliferation, apoptosis and cell adhesion. The relationship between ABL and BCR-ABL Western blots using the anti-phosphotyrosine antibody is explored.

At this point we revise all themes discussed and then decide upon the diagnosis.

But what should the patient's treatment be? An alternative, in case there is a compatible donor, could be a bone marrow transplantation.

(5) How precursor cells are obtained is discussed in the chapter on cell proliferation using a video showing an apheresis donor selected for bone marrow transplantation. The cells are then cultivated *in vitro* in order to demonstrate that there are precursor cells capable of proliferation in response to stimulation using growth factors. Methylcellulose plate precursor colonies (BFU-E and CFU-GM) are shown, and the procedure and principle of the method are explained. The proteins involved in the cell cycle are described.

(6) How a normal hematopoietic cell is capable of differentiating by means of a specific stimulation is demonstrated in the chapter on cell differentiation. The differentiation of hematopoietic cells after the addition of erythropoietin in a two-phase liquid culture of mononuclear cells obtained from peripheral blood from the bone marrow donor is shown. At this point, humoral and cellular components involved in hematopoietic cell differentiation are described.

(7) Apoptosis of normal hematopoietic cells of a patient with leukemia is presented in the chapter on apoptosis using photographs of the cells stained using hematoxylin–eosin. Apoptosis of leukemic cells is delayed. The influence of the BCR-ABL protein on the regulation of the proteins of the Bcl-2 family and its anti-apoptotic action is mentioned.

However, the first line treatment for chronic myeloid leukemia is not bone marrow transplantation but an oral tyrosine kinase inhibitor.

(8) Thus, students discuss the development of chemicals which modify the structure of proteins and that are capable of inhibiting the functions of these proteins. The drug imatinib, as well as other tyrosine kinase inhibitors, is mentioned. These drugs dephosphorylate the tyrosine of the ABL protein and inhibit the deleterious function of the abnormal protein. A figure demonstrating this function is available in the internet site. The tertiary structure of the *abl* gene and the pocket with the imatinib chemical is explored. The students have the opportunity to read layman articles on the impact of the discovery of imatinib in the treatment of chronic myeloid leukemia. The aim of this last item is to demonstrate how all the knowledge they have acquired in the basic course has importance in the development of therapeutic strategies.

(9) On the last day of the course, the students discuss a paper, which they have previously read, published in Blood.[3] The article shows *in vitro* analysis of cell lines transformed with constructs of ABL mutations, which are present in patients resistant to imatinib treatment. The aim of this exercise is to review what was taught during the course, to consolidate the knowledge acquired and to show students how to analyze a paper and be up to date in the field. It is also important to analyze mutations in the secondary and tertiary structure of the ABL protein which block the binding of the tyrosine kinase inhibitor.

Results

The course has been successful since the very beginning, 13 years ago. Students who participated in the course had great motivation and all were very enthusiastic. Less than 20% of the students were absent from classes and at least three (and as many as nine) students every year were interested in starting research training in the field of hematology. At the end of each class, an interactive evaluation was performed and more than 70% of the answers were correct at each evaluation. Moreover, for their final evaluation, the students summarize in a written report, the molecular and therapeutic bases of chronic myeloid leukemia. Considering all 13 years, a median of 78% of the class scored above 5 (min 74%–max 85%), and a median of 67% scored above 7.

Discussion

The aim of 'The Cell' course is to provide a basis to understand the main aspects of normal and abnormal molecular and cellular functioning of different systems.

The clinical case, approached during the entire course, provides the student with the opportunity to acquire basic and up-to-date knowledge regarding cell structure and function. Using chronic myeloid leukemia as an integration theme, students learn about cell dynamics, including structural and biochemical aspects of cell components, such as proteins, carbohydrates and lipids, biomembranes and organelles, receptors and signal transduction, chromatin and chromosomes, gene regulation, proliferation mechanisms, migration, adhesion, differentiation and cell death among other issues. It was also important to prepare the student to understand the diagnostic and therapeutic techniques which have recently been developed or which are yet to be developed as well as to incorporate basic scientific knowledge in order to articulate diagnostic, therapeutic and prognostic practice. Moreover, the paper gives students the opportunity to analyze scientific information relevant to professional practice.

In conclusion, chronic myeloid leukemia is an excellent disease for clinical-basic integration as it comprises well known protein, cytogenetic and cell function abnormalities, has well defined diagnosis strategies and a target oriented therapeutics.

Conflicts of interest

The authors declare no conflicts of interest.

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