Targeted and Tailored Therapy in Hemato-Oncology: Vision for the 21st Century

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Although conventional chemotherapy has made major progress in the field of hemato-oncology in the last century, the patients paid a substantial price for this success and many of them succumbed either to their disease or to the complications of treatment. Several breakthroughs occurred in the last decade, leading to dramatic changes in therapeutic approach, from conventional non-specific toxic chemotherapy to newer concepts, resulting in more effective treatments with fewer and less adverse effects. This was achieved by applying new concepts, mainly those of targeted and tailored therapy.

The primary goal in oncology has been and always will be the prolongation of life. However, no less and sometimes even more important is to achieve this goal without substantially comprising the patients' quality of life. The art of medicine attempts to navigate successfully between these two equally important goals and to achieve both, at the same time in the same patient and at the lowest cost. The impression is that a new era is dawning, where these goals can indeed be reached.

Targeted therapy

A 50% success in the cure of aggressive lymphomas was already achieved in the early 1970s. Unfortunately, these figures were not improved upon during the next two or three decades despite many scientific and technological achievements [1]. It seemed as though chemotherapy alone had reached its maximal threshold of capacity.

Due to the limited ability of chemotherapy alone and in order to avoid the notorious side effects of conventional chemotherapy, researchers had to look for drugs that would exert their effect at the molecular level of the neoplastic process, taking advantage of recent advances in the understanding of tumor biology as well as progress in biotechnology. The goal was to find drugs capable of eradicating cancer cells without adversely affecting the neighboring healthy tissue.

These goals have already been achieved in certain hematologic malignancies and cure has become a reality. The founders of Hematology, like Thomas Hodgkin and Robert Virchow, would no doubt be astounded at the dramatic change in the prognosis of diseases like chronic myeloid leukemia, now controlled by the tyrosine kinase inhibitor imatinib; aggressive lymphoma, now cured by the monoclonal antibody rituximab; and acute promyelocytic leukemia, now eradicated by all-trans retinoic acid and arsenic trioxide. Crucial to success is a comprehensive understanding of the molecular basis of these diseases. As we learn more about the various regulators of these processes, our capacity to conquer and cure them improves.

In 1996 the first publication on imatinib appeared. Then known as CGP 57148, it is the most successful prototype of targeted therapy [2]. Based on the preclinical data, phase I/II studies were conducted in patients with chronic myeloid leukemia. These studies have been ongoing since June 1998 and have targeted chronic-phase CML patients who are resistant to interferon therapy. Side effects have been minimal, and no dose-limiting toxicities have been encountered. All patients have achieved complete hematologic responses, and cytogenetic responses have also been observed [3].

These little pills revolutionized the treatment paradigm of CML, a disease that was previously cured only by bone marrow transplantation. This drug is considered today as the penicillin of leukemia. It competes with the energy-delivering molecule ATP, on its tumor-specific receptor on the malignant cell, leading finally to the death of the leukemic cell [4]. The clinical result is almost complete response, with prolonged survival achieved solely by these pills, which do not bear the disadvantages of chemotherapy [5]. However, in contrast to the penicillin story, which was serendipitous, imatinib is the result of a well-designed scientific process. Imatinib has enabled the long-term survival of most CML patients treated solely with this oral drug.

Monoclonal antibodies are another example of targeted therapy that dramatically changed the survival of cancer patients in general. In hematology, the classic example is the introduction of rituximab to the treatment of lymphomas. In contrast to chemotherapy, monoclonal antibodies can target tumor cells by recognizing cell surface antigens. Ideally, monoclonal antibodies target antigens specific to the tumor, with little or no effect on normal cells [6].

Several well-designed clinical trials showed an increase of 10–15% in the survival of patients with aggressive B cell lymphoma by the addition of rituximab to chemotherapy alone, approaching a survival rate similar to that of the general normal population [7,8]. Improved results in terms of disease-free survival and even overall survival were also recently shown for follicular lymphoma [9,10].

The concept of monoclonal antibodies was taken one step forward by the binding of radioisotopes like ytrium or iodine to the naked antibody. Through a crossfire effect, radiation delivered to

CML = chronic myelocytic leukemia

targeted antigen-positive cells allows penetration into bulky tumors and neighboring tumor cells [11-14].

Tailored therapy

Another tool to improve treatment success is by improving the diagnostic ability. The development of highly sensitive diagnostic techniques can lead to an accurate identification of patients with early disease, patients who belong to subtypes with more aggressive behavior, and patients with residual active disease who might benefit from intensified treatment for complete eradication of the residual tumor.

Modern diagnostic tools include mainly techniques that use specific molecular or metabolic characteristics of the tumor cell. To mention a few: conventional cytogenetics, fluorescence *in situ* hybridization analysis, flow cytometry, microarray and chip analysis, real-time polymerase chain reaction, and the fluorodeoxyglucose-based positron emission tomography. With the FISH technique, chromosomal deletions or translocations are easily demonstrated, and by applying the PCR technique even a single leukemic cell among a million normal cells can be detected. With the microarray technique, genes that are differentially expressed in different subtypes of hematologic malignancies can be identified and, furthermore, different risk subgroups of the same disease can be recognized.

PET/CT is an imaging technology that takes advantage of the principle that tumor cells use glucose for their metabolic activity. This leads to easy identification of tumoral sites. During the last few years, PET/CT has become the diagnostic technique of choice for a much more accurate diagnosis and staging of lymphoma patients as well as a major tool for the assessment of response and for follow-up of these patients [15-17].

Allogeneic bone marrow transplantation is the foremost tool for the cure of hematologic malignancies, combining the concept of high dose chemotherapy and immunotherapy. However, the high doses of chemotherapy used led to an unacceptable rate of morbidity as well as mortality. Understanding the urgent need for a change led to a revolution in concept in the setting of bone marrow transplantation: chemotherapy doses were significantly reduced while the role of the less toxic immunotherapy increased. This approach, also known as non-myeloablative transplant, is gaining more and more popularity and will be used in tailoring treatment for hemato-oncologic patients.

Summary

Summarizing our vision of hemato-oncology in the 21st century, we believe that with time, and with the expected progress in both medicine and biotechnology, the role of non-specific chemotherapy will decrease, while that of targeted therapies will increase. Unfortunately, for most tumors chemotherapy is still the cornerstone of treatment. We should therefore focus on finding more targeted agents, better tailoring of treatments, and identifying the risk factors for cancer development and the means of prevention of – what is likely to be – the number one killer of this century.

FISH = fluorescence *in situ* hybridization
PCR = polymerase chain reaction

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