Over the past few years, the survival rate for all cancers has improved considerably.\(^1\) The improvement has been ascribed to a combination of early detection and better treatment strategies and modalities. With the advent of systemic treatment, more and more cancers are being cured, whether they were seemingly localised, or even metastatic at presentation. The improvement in survival has been for most of the part in small incremental gains; however, there have also been some quantum leaps.

A glance at the last half century reveals that by 1961, with the advent of combination chemotherapy including nitrogen mustard compounds, more than 60% patients with Hodgkin’s lymphoma (HL) could be cured.\(^2\) This outcome was improved further by using non-nitrogen mustard combination chemotherapy, which not only improved the chances of survival by almost 10%, but also significantly reduced the long-term toxic effects, such as infertility and secondary cancers.\(^3\)

Today, 80–90% of the patients diagnosed to have HL are cured of their illness.

The next major advance was the advent of cisplatin which transformed the management of certain cancers, such as the germ cell cancers; they became curable in more than 80% of patients, even when the cancer was metastatic at the time of presentation.\(^4\) To date, cisplatin-based chemotherapy remains the standard of care for these cancers.

The third major advance was the realisation that the addition of chemotherapy to surgery improved the outcomes of patients with breast cancer. Two groups working independently in the United States and Italy published landmark studies showing that the addition of chemotherapy after mastectomy improved the survival of patients with localised and locally advanced breast cancer.\(^5,6\)

The fourth major advance was the use of allogeneic transplants which were to change the outlook for patients with relapsed acute leukaemia.\(^7,8\) However, allogeneic transplant is associated with significant toxicity, including mortality, preventing its use for the majority of patients with diseases in which it has been shown to be effective.

The fifth major advance was the use of autologous stem cell transplant in patients with relapsed high grade non-Hodgkin’s lymphoma (NHL). It became the standard of care for relapsed NHL.\(^9\)

Although all these advances are considered quantum leaps, few treatment modalities have fundamentally changed the paradigm of cancer treatment. Except for the advent of cisplatin, and the use of adjuvant chemotherapy, none of these treatments or modalities changed the outlook for the majority of cancer patients, as the effects were limited either to the tumour type, or were limited by excess toxicity. Adjuvant and neo-adjuvant chemotherapies are now an integral part of the management plan for a vast majority of cancers.

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\(^1\) From Transplant to Tablets
A paradigm shift in Oncology

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In the late 1990s, two significant advances revolutionised the way cancer is treated today. The advent of anti-CD20 antibody and the antibody to the HER-2/neu protein expressed by breast cancers have significantly changed the way that B-cell lymphoma, and about 25% of breast cancers, are treated.\textsuperscript{11,12} The second major advance was the advent of a tyrosine kinase inhibitor (TKI), imatinib mesylate, which transformed the management and outcomes of chronic myeloid leukaemia (CML).\textsuperscript{12,13} Both these two types of targeted treatment, the monoclonal antibodies and the TKIs, have resulted in a paradigm shift in the management of not only the cancers for which they were initially tested, but for an ever-expanding variety of cancer types.

Tyrosine kinase (TK) is an enzyme which either activates or deactivates other proteins by transferring a phosphate molecule to tyrosine. The process is called phosphorylation, and may become uncontrolled in cancers.\textsuperscript{13} About 90 different TKs have been identified, two thirds of which are attached to trans-membrane receptors, and the rest are cytoplasmic.\textsuperscript{13} The TKs transduce signals through the cytoplasm, and are specific to cancers. For example, epidermal growth factor receptor (EGFR), a trans-membrane receptor, is closely related to c-erb B-2 oncogene, and is over-expressed in several cancers, including, breast cancer.\textsuperscript{14} TKs attached to EGFR are autophosphorylated in these cancers. Similarly, bcr-abl fusion protein, formed as a result of reciprocal translocation between long arms of chromosomes 9 and 22 in CML, is a cytoplasmic TK.\textsuperscript{15} Both types of TKs are either mutated or activated in several cancers, and have emerged as targets for TKIs, drugs specifically designed to block these TKs. A compound, previously called STI571, and now called imatinib mesylate, was first shown to inhibit the bcr-abl TK through competitive inhibition at the ATP-binding site of the enzyme, leading to inhibition of tyrosine phosphorylation, arresting the growth of the leukaemic cells, and inducing apoptosis.\textsuperscript{15}

In this issue of SQUMJ, Shaun McCann has reviewed the history of the diagnosis and management of CML, and has asked the question, whether CML is a strange disease or a paradigm for malignancy.\textsuperscript{16} It is intriguing to note that a disease characterised by abnormal white blood cells in the peripheral blood was first described even when the microscope had not been invented; the specific chromosomal translocation was defined as early as 1960, and the resultant fusion protein bcr-abl was described in 1990. The bcr-abl fusion protein is sufficient to cause CML, and the mutational studies established that phosphorylation of TK was required for oncogenic activity. Lack of technology was the limiting factor in exploitation of those discoveries and, for a long time, the treatment aimed at reducing the white blood cells in the peripheral blood, without affecting the natural history of the disease. Only interferon alpha (IFN-α) was shown to prolong survival marginally, but was associated with considerable toxicity.\textsuperscript{17} Once allogeneic transplantation became available, selected patients could be cured, but at the expense of significant mortality. Furthermore, transplantation was available to people who were otherwise fit, and had a suitable donor. It was only after developing the capacity to block the phosphorylation of the TK domain that a new form of treatment emerged. The drug received an unprecedented rapid approval by the Food and Drug Administration (FDA) authority of the USA following the publication of a phase I trial.\textsuperscript{18} This was several years before the publication of the first phase III trial,\textsuperscript{19} something considered by many as a pre-requisite for the approval of a new medicine by the FDA.

So what brought about one of the greatest practice-changing concepts in the history of malignant haematology and medical oncology? In a proof-of-principle study, escalating doses of STI571 were administered to 83 patients in the chronic phase of CML.\textsuperscript{18} All patients had failed to respond to treatment with the standard-of-care at that stage, IFN-α. Complete haematological responses were observed in 53 of 54 patients treated with a daily oral dose of more than 300 mg; cytogenetic responses occurred in 17 patients, and 7 patients had complete cytogenetic remission. Adverse events were minimal, merely nausea, myalgia, oedema, and diarrhoea. Since then, the outcome of patients with CML has changed forever. At 7 years, 86% of the patients are alive compared with a median survival of 2–3 years, just a decade ago.\textsuperscript{20}

So massive were the implications of TKIs that soon after the description of the activity of imatinib in CML, TK targets specific to other cancers were explored. Imatinib was also found to inhibit the TK associated with the c-KIT and platelet-derived growth factor (PDGFR), expressed...
on gastrointestinal stromal tumours (GIST). Metastatic GIST, so far known to be refractory to treatment, was treated with imatinib, and more than 80% of the patients receive clinical benefit. Not only did imatinib become the gold-standard of care for the treatment of metastatic GIST but it also became a model for the quest of targets in solid tumours.

TKIs have now become the standard of care for the management of several cancers and are used either in combination with cytotoxic chemotherapy in breast cancer, or as a single agent in several difficult-to-treat cancers, such as the clear cell carcinoma of the kidney, hepatocellular carcinoma, adenocarcinoma of the lung, and melanoma. Despite the advances, there are several hurdles still to be overcome. The issue of primary and acquired resistance, side effects and ever-increasing cost of medicines are real challenges, and need to be dealt with if TKIs are to have an impact on the vast majority of common cancers.

For almost half a century, the treatment of cancer sat on a three-legged stool of surgery, radiotherapy and chemotherapy. With the addition of the targeted therapy in the last decade, it now seems to be sitting on a stable chair with four legs. Over the last 10 years, a total of 33 targeted agents have been approved by the FDA for treatment of various cancers. This is in comparison with 14 cytotoxic agents, approved during the same period. The advent of imatinib and its application in CML paved the way for the change. Registries have reported a reduction in the number of transplants for CML, and in this ‘imatinib era’ patients are treated with tablets. TKIs and other targeted therapies are now being used either to cure cancers, or to convert cancer to chronic disease. CML has led the way this time. Truly, the disease has brought about a paradigm shift.

References


