Will conventional cancer chemotherapy soon become obsolete?

La chimiothérapie conventionnelle deviendra-t-elle bientôt obsolète ?

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Louis Goodman and Alfred Gilman made medical history by inducing regression of non-Hodgkin's lymphoma by administering mustine hydrochloride to patients in 1942. It became apparent for the first time that cancer could be treated with a pharmacologic agent [1]. In the late 1940s and early 1950s, nitrogen mustard alone or combined with glucocorticoids induced significant responses in lymphoid neoplasms.

By early 1960s, cure of acute leukaemias had become a reality with the introduction of antimetabolites including methotrexate, 6-mercaptopurine and cytosine arabinoside. The development of vinca alkaloids soon followed, and this expanded cancer chemotherapeutic armamentarium.

The isolation of daunorubicin in 1961 by A Di Marco at Adria Laboratories in Milan [2] was yet another breakthrough that improved on the cures of acute leukaemia. This was followed in the late 1960s by the isolation of doxorubicin by the same group. Anthracyclines were oncological breakthroughs, with overall single agent response rates exceeding 40% in treatment-naïve malignant lymphomas and acute leukaemia. Impressive response rates were also registered in ovarian and breast cancers. These agents also had major impact in treatment of myeloma, sarcoma, ovarian cancer, non-small cell lung cancer and others.

Notable other chemotherapy successes included the development of epipodophyllotoxins, platinum compounds and taxanes. Cis-platin, carboplatin and etoposide are key agents in treatment of testicular cancer, with the majority of patients cured. The platinum compounds are also effective in treatment of cancers of breast, ovary, lung, bladder, stomach and liver.

Taxanes were first recognised as important chemotherapeutic agents in the 1960s but were only put to clinical use in the early 1990s. Today paclitaxel and docetaxel are invaluable in treatment of cancers of breast, ovary, lung, bladder and others.

Targeted cancer therapy

Targeted cancer therapy dates back to the 1970s when the selective oestrogen receptor modifier, tamoxifen, showed efficacy in breast cancer treatment. The use of all-trans-retinoic acid (ATRA) in acute promyelocytic leukaemia, and trastuzumab in Her2-overexpressing breast cancer, were notable targeted therapies of the 1990s.

In the past decade, small molecule tyrosine kinase inhibitors (TKIs) have taken an increasingly important role in the treatment of cancer. These agents were developed to block intracellular signalling pathways in tumour cells, leading to deregulation of key cell functions such as proliferation and differentiation.

The excitement that greeted the introduction of imatinib, an inhibitor of BCR/ABL TK in chronic myeloid leukaemia therapy, left no doubt as to what therapeutic breakthroughs are all about. Nearly all patients with CML in chronic phase achieve complete haematologic remission with this agent, and 80–90% complete cytogenetic remission [3]. Newer TKIs with even better activity in CML, dasatinib and nilotinib have since been developed.

The successes with imatinib emboldened researchers to concentrate efforts in development of targeted compounds, namely small molecule TKIs, monoclonal antibodies and miscellaneous compounds. Oncologists have been most enthusiastic about these developments for the reasons that: (a) conventional cytotoxics had reached their peak and were not curing any more cancers; and (b) that they were also crude, unselective and toxic. Good luck. It is only in CML where BCR-ABL, targeted by Imatinib, nilotinib and dasatinib, is a single oncogenic driving mutation. Many other efforts have largely been therapeutic misadventures laced with extremely high costs. Their therapeutic activities have been modest to say the least, mainly in combination with chemotherapy.

To be fair, other successes have been exemplified by anti-Her2 therapies in combination with chemotherapy, yielding better results than single anti-Her2 agents in breast cancer [4–6]. Trastuzumab, panitumumab and matuzumab are

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notable examples, and also the anti-Her2 small molecule TKI, lapatinib. In NSABP B31 trial by Romond and colleagues, trastuzumab in combination with chemotherapy extended 3-year DFS by 87.1% compared with 75.4% for chemotherapy-only arm among patients with operable Her2-positive breast cancer. The overall survival was 94.3% compared with 91.7% for chemotherapy only-arm, and the differences were statistically significant [7].

Rituximab: The anti-CD20 monoclonal antibody, rituximab, is another success story in treatment of B-cell lymphoproliferative neoplasms, especially follicular lymphoma and diffuse large B-cell lymphoma [8,9]. The benefits have been clearly demonstrated by various studies including those by Gordon and colleagues, Hainsworth and colleagues and Witzig and colleagues [10–12].

Anti-VEGF therapy

Treatment directed against vascular endothelial growth factor receptor (VEGFR) has had mixed results. Bevacizumab, the first VEGFR-directed therapy, has been tried in several tumour types with mixed outcomes. For example, addition of bevacizumab to docetaxel and prednisone did not improve overall survival in metastatic castrate-resistant prostate cancer and was associated instead with greater toxicity [13]. Results in colorectal carcinoma have been more encouraging [14].

Newer cytotoxics

Larotaxel, a newer semisynthetic taxane from the natural compound 10-deacetyl baccatin III, extracted from the tree, *Taxus baccata*, is showing extremely encouraging results according to a study carried out by Dieras and colleagues [15]. Others are ixabepilone, an epithelone; vinflimine, a vinca alkaloid; eribulin mesylate and the alkylating agent trabectedin. Studies in women with metastatic breast cancer, who have been heavily pretreated, have demonstrated remarkable results with these agents [16–18]. Trabectedin has also shown great promise in sarcomas.

Toxicity profile

Rash, diarrhoea, skin ulcers, pleural effusions and cardiotoxicity are toxicities being experienced with targeted therapies, while many agents still retain myelotoxicity, mucositis and other side effects that bedevil conventional cytotoxic agents.

Africa, despite having vast natural resources, is the most resource-challenged continent, and patients here can hardly afford the targeted drugs. Whereas a new drug developer is

under no obligation to make drugs affordable to Africa and other low-income parts of the world, it would be prudent to justify drug costs on treatment outcome and safety parameters rather than on how much cost in research spending has been accrued even if the agent has no more than placebo effect.

Conclusion

With the foregoing, it is the contention of the author that conventional cancer chemotherapy is highly unlikely to become extinct soon.

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