



New Drugs for the Treatment of Cancer, 1990–2001

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Abstract

Between 1990 and 2001, altogether 28 new anticancer drugs were approved for use in Israel. The new agents include cytotoxic drugs, biologic compounds, and hormone therapies. Among the cytotoxic agents introduced, the taxanes, vinorelbine, gemcitabine, irinotecan, topotecan and temozolomide, represent important new drugs active in a range of solid malignancies including lung, breast, ovarian, bladder, pancreatic, and colon cancer as well as brain tumors. Epirubicin, idarubicin, and liposomal doxorubicin offer less toxic and in some instances more effective alternatives to older anthracyclines for leukemia, breast cancer, ovarian cancer and other diseases. New oral agents are offering a chance for disease palliation without the need for burdensome intravenous access. Rituximab and trastuzumab have introduced monoclonal antibody therapy to the clinic, substantially improving the treatment of patients with lymphoma and breast cancer, respectively. The first tyrosine kinase inhibitor, a molecularly targeted therapy, imatinib, was approved for use in chronic myeloid leukemia and has also shown remarkable activity in gastrointestinal stromal tumors. A variety of aromatase inhibitors have provided less toxic and more effective hormone therapy for the treatment of breast cancer. The challenge for clinicians is to optimize the use of the new available agents for their patients' benefit, and the challenge for health policymakers in Israel is to integrate the new anticancer pharmaceuticals into the basic health benefits package mandated for all citizens.

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The development of new antineoplastic drugs is a key to progress in cancer treatment. The decade of the 1990s witnessed the introduction into clinical practice of many new anticancer agents, several with activity in previously poorly responsive metastatic tumors, such as non-small cell lung cancer, colon cancer, kidney cancer, melanoma and pancreatic cancer. In order to highlight the progress in cancer chemotherapy over the past decade we review here the drugs for cancer treatment that were approved for use by the Ministry of Health in Israel between 1990 and 2001 [1]. The new agents include cytotoxic drugs, biologic and immunologic compounds, as well as hormones [Tables 1–3].

Cytotoxic drugs

Mitotic spindle poisons

The taxanes, paclitaxel and docetaxel, are derivatives of natural products that prevent mitosis by promoting microtubule assembly

and inhibiting microtubule depolymerization to free tubulin [2]. Paclitaxel was originally derived from the bark of the Pacific yew tree, *Taxus brevifolia*, and docetaxel was synthesized from a renewable and more abundant source, the needles of the tree *Taxus baccata* [3]. Paclitaxel can now be synthesized from more readily available sources, solving what was originally a very difficult supply problem [4]. Paclitaxel and docetaxel have shown activity in a wide range of tumor types, and the indications for their use will probably rapidly expand. The introduction of the taxanes into clinical practice has been a major step forward in the treatment of ovarian, breast and lung cancers. The combination of paclitaxel-cisplatin was shown in a randomized trial to be superior to the previous standard of cyclophosphamide-cisplatin for the treatment of advanced ovarian cancer. In metastatic non-small cell lung cancer, paclitaxel-cisplatin was shown to be more active than the previous standard of etoposide-cisplatin. Docetaxel was shown to be the first agent to yield meaningful responses in relapsed advanced NSCLC. In metastatic breast cancer, docetaxel has replaced doxorubicin as the most active single agent; and for patients whose tumors overexpress the HER2 antigen (HER-2 positive), paclitaxel administered concomitantly with trastuzumab, a monoclonal antibody against HER-2, has become a standard of care. In order to determine how best to integrate taxanes into the adjuvant treatment of early-stage breast cancer, several multi-institutional United States and international trials are now underway [2].

The main toxicities of paclitaxel are myelosuppression, myalgias, neuropathy and alopecia. It must be administered in non-polyvinyl chloride tubing because of the organic solvent in which it is dissolved. In addition, premedication with steroids and antihistamines must be given to prevent hypersensitivity reactions. Docetaxel causes myelosuppression, alopecia, and – to a lesser extent than paclitaxel – neuropathy. In addition, docetaxel causes a syndrome of fluid retention, manifested by peripheral edema and pleural effusions and probably caused by a capillary leak syndrome, which can be prevented by giving steroids prior to treatment and continuing for 1–2 days after treatment. Docetaxel causes nail changes that can sometimes be avoided by having the patients soak their fingers in ice-cold water during the infusion [2].

NSCLC = non-small cell lung cancer

Table 1. Cytotoxic therapy: new agents, 1990–2001

Class of drug	Generic name	Trade name, manufacturer	Diseases [1]
Mitotic spindle poisons	Paclitaxel	Taxol, Bristol-Myers- Squibb, USA; Biotax, Napro Biotherapeutics, USA; Medixel, Tauro, Israel	Cancers of ovary, breast, lung, Kaposi's sarcoma
	Docetaxel	Taxotere, Aventis, France	Cancers of ovary, breast, lung
	Vinorelbine	Navelbine, Pierre Fabre, France	Lung and breast cancer
Topoisomerase inhibitors	Irinotecan	Campto, Aventis, France	Colorectal cancer
	Topotecan	Hycamtin, Smith-Kline Beecham, USA	Ovarian and small cell lung cancer
Anthracyclines	Epirubicin	Farmorubicin, Pharmacia, Italy	Breast, lung, ovarian, gastric, bladder cancer, soft tissue sarcoma
	Doxorubicin, liposome encapsulated	Caelyx, Alza, USA	AIDS-related Kaposi's sarcoma, ovarian cancer
	Idarubicin	Zavedos, Pharmacia, Italy	ALL, acute non-lymphocytic leukemia
Antimetabolites	Fludarabine	Fludara, Schering AG, Germany	CLL
	Cladribine (2-CdA)	Leustatin, Cilag AG, Switzerland	Hairy cell leukemia, CLL
	Capecitabine	Xeloda, Hoffman LaRoche, USA	Breast and colon cancer
	Tegafur-uracil	UFT, Bristol-Myers-Squibb, USA	Colon cancer
	Gemcitabine	Gemzar, Eli-Lilly, France	Cancers of pancreas, lung, bladder
Alkylating agents	Fotemustine	Muphoran, Thissen, Belgium	Melanoma
	Temozolomide	Temodal, Schering-Plough, USA	Malignant glioma
Topical agent	Miltefosine	Miltex, Asta Medica, Germany	Breast cancer
	Carmustine (implant)	Gliadel wafer, Aventis, France	Glioblastome multiforme

Vinorelbine is a semi-synthetic vinca alkaloid that interferes with polymerization of tubulin, causing dissolution of microtubules and preventing mitosis.

Clinical trials have shown that vinorelbine is active as a single agent or in combination with cisplatin in advanced NSCLC, with superior response rates and survival when compared to therapies containing older drugs. Vinorelbine has also been effective in metastatic breast cancer when used as a single agent or together with doxorubicin or 5-fluorouracil. Hodgkin's disease and small cell lung cancer are also responsive to vinorelbine, as shown in early trials [5].

Vinorelbine's major dose-limiting toxicity is myelosuppression. Phlebitis at the site of infusion may sometimes occur. Neuropathy, usually mild, is noted in up to 30% of patients. Vinorelbine requires no premedication or hydration and can be given as a short infusion lasting 5–10 minutes [5].

Topoisomerase inhibitors

Within the cell nucleus the lengthy DNA double helix is twisted and supercoiled. This tightly packed physical configuration must be loosened in order for DNA replication or RNA transcription to proceed. Topoisomerase I is an enzyme that binds to DNA during replication, cutting one of the strands to relax the torsion of the supercoiled helix, and subsequently resealing the single-strand break. Another enzyme, topoisomerase II, causes double-stranded DNA breaks that enable newly synthesized DNA to pass through the parent double helix without getting tangled. The first anticancer agent that inhibited topoisomerase I was camptothecin, an alkaloid extract of the tree *Camptotheca acuminata*. Toxicity and solubility problems precluded its clinical use. Two analogues of camptothecin, irinotecan and topotecan, were developed and introduced into

clinical practice in the last decade. Both drugs prevent topoisomerase I from resealing the DNA break, resulting in a double-stranded DNA break and cell death [6].

Irinotecan, also known as CPT-11, has shown activity in a variety of tumors, including gastrointestinal, ovarian, and lung cancers, as well as malignant lymphomas and brain tumors. It has been most thoroughly investigated in colorectal cancer. CPT-11 can induce responses in patients who have relapsed on standard 5-fluorouracil plus leucovorin treatment. The combination of CPT-11 given as an infusion over 30 minutes along with 5-FU and leucovorin as bolus injections weekly for 4 weeks every 6 weeks (the Saltz regimen) has improved results of first-line therapy of metastatic colorectal cancer, as shown by a randomized trial [7]. In two separate clinical trials the Saltz regimen was compared to 5-FU-leucovorin as adjuvant therapy and in the metastatic setting to oxaliplatin, an investigational drug, combined with either CPT-11 or 5-FU-leucovorin. Patient accrual was stopped because of mortality in excess of expected on the Saltz regimen arms of both the adjuvant and metastatic trials, 2.2% and 4.8%, respectively. An independent review panel suggested that close clinical monitoring and aggressive early treatment of toxicities were essential in the use of this regimen but did not recommend abandoning it [8]. The dose-limiting toxicities of CPT-11 are neutropenia and diarrhea, usually beginning several days after therapy. Often the diarrhea can be aborted by prompt aggressive treatment with loperamide. A cholinergic-like syndrome, which consists of diaphoresis, abdominal cramps, diarrhea, hyperlacrimation and rhinorrhea, occurs in up to 79% of patients at the time of drug infusion or shortly afterwards. The syndrome responds quickly to atropine, and the use of prophylactic atropine in subsequent

5-FU = 5-fluorouracil

treatments will prevent its recurrence. Nausea, vomiting, fatigue and alopecia commonly occur [6].

Topotecan, although similar in structure and mechanism of action to irinotecan, has a different spectrum of antitumor activity and is given in a different schedule. It is now a standard treatment option for second-line therapy of ovarian cancer and is being investigated as a front-line agent in combination with other drugs. In small cell lung cancer, topotecan was shown in a randomized trial of second-line therapy to be as effective as the previous standard combination of cyclophosphamide, vincristine and doxorubicin, but less toxic. Clinical trials are assessing the integration of topotecan into first-line therapy for small cell lung cancer. Topotecan crosses the blood-brain barrier, making it a particularly attractive drug for this disease, with its propensity for central nervous system spread. The main toxicities of topotecan are neutropenia and thrombocytopenia. Topotecan is administered as a brief infusion 5 days in a row every 4 weeks [6].

Anthracyclines

Anthracyclines are used in the treatment of a wide range of malignancies and are among the most active drugs in the treatment of breast cancer. Among their mechanisms of action is inhibition of topoisomerase II. The use of doxorubicin, the prototype drug of this class, is sometimes limited by cardiotoxicity. Epirubicin is an analogue of doxorubicin, which is less cardiotoxic at equivalent doses. It is not clear whether the cardiac advantage of epirubicin is maintained at doses of equivalent efficacy of antitumor action [9]. Myelotoxicity is the other major toxicity. Epirubicin, when given in escalated doses in metastatic breast cancer, shows a dose-response relationship. In Europe and Canada it has largely replaced doxorubicin in the adjuvant setting as well as in the treatment of metastatic breast cancer. The introduction of dexrazoxane as a cardiac protector has diminished the importance of the possible cardiac advantage of epirubicin over doxorubicin; and in Israel, as in the U.S, doxorubicin is still the predominant anthracycline used in breast cancer. The topoisomerase II inhibitor class of drug has been associated with the later development of acute myelogenous leukemia. While there may be a slightly higher rate of acute myelogenous leukemia after epirubicin than after doxorubicin, the rates are low. Different adjuvant trials in breast cancer have shown AML rates of 1.1% with an epirubicin-containing regimen during 5 years of follow-up, and rates of 1.5% and 0% with doxorubicin regimens in trials with 10 and 13 years of follow-up, respectively [10].

Idarubicin is a synthetic anthracycline that has been shown to be more effective in the treatment of AML than daunorubicin, the previous standard anthracycline in leukemia therapy. Idarubicin-containing regimens for acute lymphoblastic leukemia have also been introduced. A possible mechanism for its efficacy is that *in vitro* it is less sensitive to p-glycoprotein-mediated drug efflux (the mechanism of multidrug resistance) than is daunorubicin [11]. Unlike other anthracyclines, idarubicin can be administered orally. An all-oral idarubicin-containing chemotherapy program for low

grade non-Hodgkin's lymphoma has been reported with a high response rate and mild toxicity [12].

Another approach to decrease the toxicity and increase the efficacy of anthracyclines has been encapsulation of the parent drug, either doxorubicin or daunorubicin, in a pegylated liposome, which is a liposome with segments of polyethylene glycol attached to its surface. Because of the encapsulating pegylated liposome, the drug has an increased plasma half-life (due to prolonged time to reticuloendothelial system uptake) as well as an increased delivery of drug to tumor in comparison to the non-encapsulated drug. Investigators in Israel have been instrumental in the development of pegylated liposomal doxorubicin [13]. Liposomal doxorubicin was shown to yield higher response rates and less alopecia, nausea and vomiting than the combination of doxorubicin, bleomycin and vincristine in the therapy of acquired immunodeficiency-related Kaposi's sarcoma. The degree of myelosuppression was similar for both regimens. The liposomal doxorubicin produced an acute infusion reaction of flushing, dyspnea and hypotension in a few patients in that trial, but further episodes in those patients were prevented by premedication with steroids and antihistamines [14]. Slowing the infusion rate has been shown to be the best way of reducing the risk of an acute infusion reaction [13]. In a study of 42 patients treated with cumulative liposomal doxorubicin doses of greater than 500 mg/m², cardiotoxicity was evaluated by endomyocardial biopsies and multigated acquisition cardiac isotopic scans. A much lower rate of cardiotoxicity was found than would have been expected with comparable doses of conventional doxorubicin [15]. Liposome-encapsulated doxorubicin has shown activity in ovarian cancer refractory to previous chemotherapy and is under investigation in the treatment of a number of other tumor types [12,14]. It is now approved by the Ministry of Health for use in platinum- and taxane-resistant ovarian cancer as well as for AIDS-related Kaposi's sarcoma [1].

Antimetabolites

Gemcitabine is a pyrimidine analogue that represents the first advance in the treatment of pancreatic cancer since the introduction of 5-FU over 40 years ago. In a randomized trial, gemcitabine yielded significantly greater relief of cancer-related symptoms and a modest gain in survival when compared to 5-FU [16]. Gemcitabine is approved for use in NSCLC and bladder cancer, as well as pancreatic cancer. A randomized trial demonstrated that for locally advanced or metastatic NSCLC, the combination of gemcitabine-cisplatin was superior to the former standard treatment of etoposide-cisplatin [17]. In metastatic bladder cancer, a large randomized trial has shown that gemcitabine-cisplatin is at least as effective and is less toxic than the widely used regimen of cisplatin, methotrexate, doxorubicin and vinblastine [18]. In addition to its activity in a wide spectrum of solid tumors, gemcitabine was shown to induce responses in patients with recurrent heavily pretreated lymphoma [19]. Gemcitabine is administered by a 30 minute infusion and causes few acute side effects. Myelosuppression is the dose-limiting toxicity [16-19].

Fludarabine and cladribine (2-chlorodeoxyadenosine, 2-CDA) are purine nucleoside analogues. Fludarabine is officially approved

AML = acute myelogenous leukemia

for use by the Ministry of Health for relapsed chronic lymphocytic leukemia, but it has become an important agent in the treatment of low grade lymphomas. In CLL, fludarabine as a first-line agent yields longer remissions and higher response rates than the standard therapy of chlorambucil, although overall survival is the same. Besides causing myelosuppression, fludarabine causes T lymphocyte depletion as well as neutropenia, which can lead to opportunistic infections. Fludarabine is administered intravenously in divided doses for 3 to 5 days. An oral formulation is now available to reduce the inconvenience of multiple infusions [20]. Cladribine has replaced interferon and splenectomy as the treatment of choice for hairy cell leukemia. Deoxycoformycin can also be used but it is not as readily available as cladribine. One course of a 7 day infusion of cladribine can put most patients with hairy cell leukemia into complete remission. The major side effects are myelosuppression and infections. Late relapses occasionally occur, but most patients do very well [21].

Capecitabine and tegafur-uracil are oral antimetabolites that entered clinical use at the end of the 1990s. The pharmacokinetics of the two oral agents resemble that of continuous intravenous 5-FU, which has a different mechanism of action than that of intermittent bolus 5-FU. Some tumors have a higher response rate to continuous 5-FU than to intermittent bolus 5-FU. The major limitation of continuous 5-FU is the inconvenience and technical problems of portable infusion pumps and intravenous access. After oral administration of UFT, tegafur, also known as ftorafur, is converted into 5-FU in the liver. The other component of UFT, uracil, competitively inhibits dihydropyrimidine-dehydrogenase, the main catabolizing enzyme of 5-FU, prolonging the plasma half-life of the 5-FU. The combination of UFT and oral leucovorin has become an alternative to intravenous 5-FU and leucovorin in colon cancer, although toxicities of myelosuppression and diarrhea are still encountered. Capecitabine is converted to 5-FU by thymidine phosphorylase, which is present in higher concentrations in tumors than in normal tissues. Prior to reaching the tumor it undergoes metabolism in the liver. Thus the gastrointestinal tract is exposed only to the relatively inactive parent drug. Capecitabine has been investigated extensively in breast and colon cancer and is approved for use in Israel for both of those diseases. Breast cancer patients, who can still be candidates for palliative chemotherapy after progression on two or more treatment regimens, often welcome oral therapy after months or years of intravenous infusions. The main side effects are diarrhea and hand-foot syndrome (palmar-plantar erythrodysesthesia) [22].

Alkylating agents

Fotemustine is a nitrosourea-type alkylating agent. All alkylating agents exert their cytotoxic effect via covalently binding to DNA. During the last few decades, alkylating compounds were developed with variations of the non-alkylating part of the molecule that affect pharmacokinetics, therapeutic effect, and toxicity. Fotemustine was found to be somewhat active in the therapy of melanoma, a disease

resistant to most chemotherapy [23]. Temozolomide, the first of a new generation of alkylating agents to enter clinical use, crosses the blood-brain barrier and does not require hepatic activation. Trials with this agent in the treatment of usually chemotherapy-resistant brain tumors have shown promising results. It is given orally, for 5 consecutive days every 4 weeks, and has very manageable side effects – mild myelosuppression and nausea [24]. Temozolomide has been approved for use in glioblastoma multiforme or anaplastic astrocytoma after recurrence or progression after standard therapy (surgery, radiotherapy) [1].

Topical agents

Carmustine, or BCNU, an established systemic therapy, is a nitrosourea-type alkylating agent used in glioblastoma multiforme and is now available in wafer form that can be implanted in the brain at the time of resection of malignant gliomas. While the advantage of implanting BCNU wafers has not been conclusively demonstrated, it represents an interesting approach to the treatment of brain tumors, particularly relapsed glioblastoma multiforme [25]. Miltefosine is a topical treatment for the palliation of cutaneous metastases of breast cancer. It is an alkylphosphocholine with a fatty acid-like backbone that affects cellular enzymes involved in phospholipid turnover, disrupting and destabilizing cell membranes. There are generally no systemic side effects and skin reactions can be controlled with dose adjustments and symptomatic care [26]. This is a welcome addition to the armamentarium of breast cancer palliation as patients often have very bothersome skin metastases late in their course of illness but cannot tolerate systemic agents because of heavy pretreatment.

Immunologic and biologic therapy

Monoclonal antibodies

A novel approach to drug treatment of cancer that reached the clinic in the last decade is the use of monoclonal antibodies. CD-20 is a cell surface antigen expressed on normal B lymphocytes and on 90% of B cell lymphomas. Rituximab is a chimeric anti-CD-20 antibody consisting of a human immunoglobulin G1 kappa antibody with mouse variable regions. It is currently approved for use in low grade B cell lymphoma. Completed and ongoing clinical trials may soon establish rituximab as a new standard of therapy for aggressive B cell lymphomas to be used along with established chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine and prednisone. Toxicities are those of immediate infusion reactions such as fever, chills, nausea, hypotension and bronchospasm, which are usually controlled by slowing the rate of infusion. Patients are administered antihistamines and antipyretics on the day of treatment to minimize the side effects. The treatment program in relapsed low grade lymphoma consists of four once-weekly drug infusions [27].

Trastuzumab is a recombinant humanized monoclonal antibody against HER2, a growth factor receptor. HER2 is overexpressed in about 25% of breast cancers as well as in other epithelial malignancies. In early clinical trials trastuzumab showed modest activity as a single agent in heavily pretreated HER2-positive breast cancer patients. In a trial testing the combination of trastuzumab

CLL = chronic lymphocytic leukemia
UFT = tegafur-uracil

Table 2. Immunologic and biologic therapy: new agents, 1990–2001

Class of drug	Generic name	Trade name, manufacturer	Diseases [1]
Monoclonal antibodies	Rituximab	Mabthera, Hoffman-LaRoche, Switzerland	Low grade or follicular B cell lymphoma
	Trastuzumab	Herceptin, Genentech, USA; Hoffman-LaRoche, Switzerland	HER2-positive breast cancer
Biologic response modifier	Aldesleukin	Proleukin, Chiron, Holland	Renal cell cancer, melanoma
Tyrosine kinase inhibitor	Imatinib (STI571)	Glivec, Novartis, USA	CML, GIST
Differentiating agent	Tretinoin	Vesanoid, Hoffman-LaRoche, Switzerland	APL

and chemotherapy, 469 patients with metastatic HER2-positive breast cancer were treated with doxorubicin or paclitaxel chemotherapy (depending on whether they had received adjuvant doxorubicin), and randomized at the start of treatment to cytotoxic therapy alone or cytotoxic therapy plus trastuzumab. The combination yielded significantly longer survival and a higher response rate. The only major additional toxicity was an increase in cardiotoxicity, particularly in the group that received doxorubicin concomitantly with the antibody [28]. Trastuzumab has now entered clinical trials for adjuvant therapy of breast cancer and is being investigated in non-small cell lung, prostate and ovarian cancers. It is administered on a weekly basis, frequently in combination with a taxane, with the first infusion given for 90 minutes and then subsequent doses for 30 minutes. Other than the rare hypersensitivity reaction, there are no acute toxicities and trastuzumab does not exacerbate the myelosuppression of chemotherapy [28,29]. Because of cardiotoxicity, concomitant administration of doxorubicin with trastuzumab is not recommended [30].

Biologic response modifier: aldesleukin

Interleukin-2 is a cytokine (protein) produced by T lymphocytes that stimulates the proliferation and activation of natural killer and T lymphocytes, which should theoretically aid in the destruction of malignant cells. Human recombinant IL-2 (aldesleukin) was developed and approved for use in the treatment of metastatic melanoma and renal cell carcinoma, diseases for which no chemotherapeutic agent has shown consistent activity. In both kidney cancer and melanoma, aldesleukin yields about a 15% response rate. Approximately one-third of the responses are complete and usually durable, so the few patients who benefit from therapy are often cured. High dose IL-2 as used in the early trials causes the release of multiple cytokines, which leads to the major toxicity – the capillary leak syndrome – manifested by pulmonary edema, and eventually multiorgan failure. Lower dose regimens, many in combination with interferon and/or cytotoxic agents, are being investigated in the hope of maintaining or improving response rates and decreasing toxicity [31].

Differentiating agent: tretinoin

Retinoids are compounds that bind to receptors in the cell nucleus, leading to cell differentiation and inhibition of proliferation. Most

patients with acute promyelocytic leukemia can be put in complete clinical remission by daily oral administration of all-trans retinoic acid (tretinoin). Side effects include headache, dry skin, xerostomia and itching. Leukocytosis and transient elevation of liver enzymes are often observed. Up to 40% of patients with APL being treated with ATRA develop a syndrome of fever, respiratory distress, pulmonary infiltrates and effusions. The syndrome is usually reversible with steroid treatment. Because the response to ATRA usually lasts only 3–5 months, with resistance rapidly developing, ATRA is stopped soon after complete remission is achieved and conventional chemotherapy regimens are administered [32].

Tyrosine kinase inhibitor: imatinib

Molecular targeting of therapy has become a reality with the introduction of the first tyrosine kinase inhibitor into clinical practice. In both CML and GIST, imatinib, a rationally developed tyrosine kinase inhibitor, also known as STI-571, has shown a remarkable level of antitumor activity. In CML, the abnormal protein Bcr-Abl, resulting from the translocation of the *cAbl* gene on chromosome 7 to the *bcr* gene on chromosome 9, is a tyrosine kinase essential for the malignant transformation of the myeloid cell. It facilitates the phosphorylation of tyrosine residues by removing a phosphate from adenosine triphosphate. Imatinib blocks the binding of ATP to the Bcr-Abl protein and prevents phosphorylation. Treatment of CML patients with imatinib has resulted in normalization of white blood cell counts in most patients treated in the chronic phase and 10% achieved a complete cytogenetic response. When CML patients in blast crisis were treated, a group who usually do not respond well to chemotherapy, major responses were seen in 55% of patients, including an 11% complete remission rate with normal blood counts. The tyrosine kinases c-kit and PDGF-R are also inhibited by the drug. GIST, for the most part refractory to chemotherapy, often express c-kit. In these c-kit-positive GIST, imatinib induced impressive clinical responses. Further investigations in other tumors expressing c-kit and PDGF-R are proceeding and other tyrosine kinase inhibitors are being developed [33].

APL = acute promyelocytic leukemia
 ATRA = all-trans retinoic acid
 CML = chronic myelogenous leukemia
 GIST =gastrointestinal stromal tumors
 ATP = adenosine triphosphate

IL-2 = interleukin-2

Table 3. Hormonal therapy: new agents, 1990–2001

Mode of action	Generic name	Trade name, manufacturer	Diseases [1]
Non-steroidal aromatase inhibitor	Anastrozole	Arimidex, Zenaca, UK	Breast cancer
	Letrozole	Femara, Novartis, Switzerland	Breast cancer
Steroidal aromatase inhibitor	Exemestane	Aromasin, Pharmacia, Italy	Breast cancer
	Formestane	Lentaron, Novartis, Switzerland	Breast cancer
Non-steroidal anti-androgen	Bicalutamide	Casodex, Zenaca, Switzerland	Prostate cancer
	Flutamide	Eulexin Schering-Plough, USA; Flutamide-Teva, Pharmachemie BV, Holland	Prostate cancer

Hormonal therapy

Aromatase inhibitors

Estrogen receptor-positive breast cancers often respond to hormonal treatment. Since the 1970s, tamoxifen, a selective estrogen receptor modulator, has been the first-line of hormonal therapy. An alternate way to block estrogen effects is to prevent estrogen production. Aromatase is the enzyme that catalyzes the conversion of androstenedione and testosterone to estrone and estradiol in the ovaries, breast stroma and tumor, fat, muscle and skin. Inhibition of aromatase can significantly reduce estrogen levels in post-menopausal women. The first of the aromatase inhibitors, aminoglutethimide, had unpleasant side effects, yet was in use for years as a second-line hormonal therapy. The new aromatase inhibitors are all superior to aminoglutethimide in terms of toxicity, and some trials have also shown increased efficacy. In addition, the new agents have demonstrated improved efficacy and less toxicity when compared with megestol acetate, a progestational agent frequently used in the past as a second-line hormonal agent. They are not indicated for use in women with functioning ovaries because of competition to bind the aromatase complex by the high premenopausal levels of androstenedione. In addition, even if there is an initial drop in circulating estrogen, high levels of gonadotropins released by the pituitary in response to decreased estrogen levels will cause an increase in aromatase production in functioning ovaries, resulting in estrogen synthesis despite the presence of the inhibiting drug [34].

Formestane, the first available new-generation aromatase inhibitor, must be given intramuscularly, while the other new inhibitors are given orally. Exemestane, as well as formestane, are steroidal aromatase inhibitors. Letrozole and anastrozole are non-steroidal inhibitors and reversibly block aromatase function. Steroidal inhibitors irreversibly block aromatase and may also affect bone and lipid metabolism. Exemestane has shown activity in metastatic breast cancer as third-line hormonal therapy, after disease progression on tamoxifen and a non-steroidal aromatase inhibitor. The side effects of all these agents are similar – hot flashes, fatigue, headaches, nausea and vomiting – and are usually infrequent and mild. The new aromatase inhibitors have not been compared with each other in randomized trials so there is no clinical evidence for the superiority of any one of them over the other [34]. The aromatase inhibitors are in the process of replacing tamoxifen as first-line hormonal therapy. Two clinical trials have recently been published showing increased time to tumor progres-

sion with anastrozole and letrozole, respectively, compared with tamoxifen in metastatic breast cancer [35,36]. Clinical trials are in progress worldwide to test sequential therapy of tamoxifen and aromatase inhibitors in various permutations as adjuvant therapy in early breast cancer [36].

Anti-androgens

The 1980s witnessed the introduction of luteinizing hormone-releasing hormone analogue therapy of prostate cancer as an alternative to orchiectomy in order to reduce androgen levels. These agonists are now available in extended-release preparations to enable treatment every 3 months instead of monthly. Another pharmacologic approach to the lowering of androgen effects is the blockade of androgen receptors to prevent testosterone effects. Combined LHRH agonist and anti-androgen therapy is often given because the blockade with anti-androgen therapy alone is usually incomplete. In the 1990s, two non-steroidal competitive inhibitors of testosterone at the level of the androgen receptor were introduced, flutamide and bicalutamide [37]. The non-steroidal agents do not affect testosterone secretion, as does the older steroidal anti-androgen drug, cyproterone acetate; therefore when used as a single agent potency is sometimes preserved. The major toxicities of flutamide are liver damage and diarrhea. Bicalutamide often causes gynecomastia, unless the patient receives prophylactic breast irradiation, and a somewhat lower incidence of hepatotoxicity and diarrhea than does flutamide. One trial in locally advanced and metastatic prostate cancer that compared bicalutamide therapy alone to flutamide plus an LHRH agonist showed similar progression – free and overall survival in both arms but better quality of life and less toxicity in the bicalutamide group. There was, however, a trend for longer survival in the patients with metastatic disease in the combined treatment group. Various combinations and sequences of hormonal therapies are being investigated in prostate cancer, in the metastatic, adjuvant and neoadjuvant settings [38].

Conclusion

Between 1990 and 2001 more than a score of new drugs were added to the array of anticancer pharmaceuticals available to the clinician in Israel. We did not report on the inclusion of the new drugs in the “basket” of health services that the Ministry of Health requires the

LHRH = luteinizing hormone-releasing hormone

health funds to provide their members, nor did we list all of the Ministry's criteria for the use of each drug in indicated diseases. For example, capecitabine monotherapy is approved by the Ministry of Health for use in breast cancer, only after disease progression with anthracyclines and taxanes [1]. Integration of emerging cancer therapies into the basic package of healthcare benefits provided to all citizens in Israel will continue to be a major challenge for those charged with allocating the available healthcare resources. Many more agents are in the process of development and will eventually be introduced into clinical practice. New analogues of cisplatin are being developed, such as oxaliplatin, which is being investigated most extensively in colorectal cancer and may represent an improvement in the treatment of that disease [8]. New classes of drugs with novel mechanisms of actions are being reported. The success of the first tyrosine kinase inhibitor, imatinib, represents a breakthrough in the use of rationally developed non-cytotoxic, molecular based therapy. Effective therapy in the blast crisis of CML and GIST, two conditions refractory to standard treatments, is one of the most striking accomplishments in cancer treatment over the past decade [33]. Other new approaches have not yet entered clinical practice but are in clinical trial. Inhibition of tumor blood vessel formation (angiogenesis) is a paradigm of action against cancer that was not clinically exploited until recently. Monoclonal antibodies to inhibit angiogenesis are now being investigated [39]. Matrix metalloproteinase inhibitors can prevent tumor cells from growing into surrounding stroma, as well as inhibiting angiogenesis, and are the subject of intense study [40]. Radiolabeled antibodies are exhibiting responses in chemotherapy-resistant hematologic malignancies and may be superior to the current non-radiolabeled antibody treatment [30].

Cancer patients in 2002 have more and better treatment options than cancer patients had in 1990. It is up to clinicians to optimize the use of new therapies for the benefit of today's patients and to participate in clinical trials that will enable the continuing development of new and improved cancer chemotherapy for the patients of the future.

References

1. <http://www.health.gov.il/units/pharmacy>.
2. Crown J, O'Leary M. The taxanes: an update. *Lancet* 2000;355:1176-8.
3. Cortes JE, Pazdur R. Docetaxel. *J Clin Oncol* 1995;13:2643-55.
4. Chu E, Grever MR, Chabner B. Cancer drug development. In: De Vita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology*, Vol. 1, 6th edn. Philadelphia: Lippincott Williams & Wilkins, 2001:345-56.
5. Gregory RK, Smith IE. Vinorelbine - a clinical review. *Br J Cancer* 2000;82:1907-13.
6. Rothenberg ML Topoisomerase I inhibitors: review and update. *Ann Oncol* 1997;8:837-55.
7. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan study group. *N Engl J Med* 2000;343:905-12.
8. Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S. Mortality associated with irinotecan plus bolus fluorouracil/leucovorin. Summary findings of an independent panel. *J Clin Oncol* 2001;19:3801-7.
9. Ryberg M, Nielsen D, Skovsgaard T, Hansen J, Jemsen BV, Dombernowsky P. Epirubicin cardiotoxicity: an analysis of 469 patients with metastatic breast cancer. *J Clin Oncol* 1998;16:3502-8.
10. French Adjuvant Study Group. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. *J Clin Oncol* 2001;19:602-11.
11. Bassan R, Chiodini B, Lerede T, et al. The role of idarubicin in adult acute lymphoblastic leukemia: from drug resistance studies to clinical application. *Leuk Lymphoma* 1997;26(Suppl 1):89-97.
12. Taylor PR, Jackson GH, Galloway MJ, et al. Primary treatment of low-grade non-Hodgkin's lymphoma using an all oral anthracycline-containing regimen, chlorambucil, idarubicin, dexamethasone (CID) - a phase II study. *Cancer Chemother Pharmacol* 2000;46:63-8.
13. Uziely B, Jeffers S, Isacson R, et al. Liposomal doxorubicin: antitumor activity and unique toxicities during two complementary phase I studies. *J Clin Oncol* 1995;13:1777.
14. Northfelt DW, Dezube BJ, Thommes JA, et al. Pegylated-liposomal doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. *J Clin Oncol* 1998;16:2445-51.
15. Safra T, Muggia FM, Jeffers S, et al. Pegylated liposomal doxorubicin (doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m². *Ann Oncol* 2000;11:1029-33.
16. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403-13.
17. Cardenal F, Lopez-Cabrero MP, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 1999;17:12-18.
18. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;18:3068-77.
19. Savage DG, Rule SAJ, Tighe M, et al. Gemcitabine for relapsed or resistant lymphoma. *Ann Oncol* 2000;11:595-7.
20. Rae KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N Engl J Med* 2000;343:1750-7.
21. Tallmann MS, Peterson LC, Hakimian D, Gillis S, Polliack A. Treatment of hairy-cell leukemia: current views. *Semin Hematol* 1999;36:155-63.
22. Sulkes A. From 5 fluorouracil to the new oral fluoropyrimidines: a brief overview of four decades of clinical investigation. *IMAJ* 2001;3:278-81.
23. Daponte A, Ascierto PA, Gravina A, et al. Cisplatin, dacarbazine, and fotemustine plus interferon alpha in patients with advanced malignant melanoma. A multicenter phase II study of the Italian Cooperative Oncology Group. *Cancer* 2000;89:2630-6.
24. Friedman HS, Kerby T, Calvert H. Temozolomide and treatment of malignant glioma. *Clin Cancer Res* 2000;6:2585-97.
25. Engelhard HH. The role of interstitial BCNU chemotherapy in the treatment of malignant glioma. *Surg Neurol* 2000;5:458-64.
26. Leonard R, Hardy J, van Tienhoven G, et al. Randomized, double-blind, placebo-controlled, multicenter trial of 6% miltefosine solution, a topical chemotherapy in cutaneous metastases from breast cancer. *J Clin Oncol* 2001;19:4150-9.
27. Vose JM, Link BK, Grossbard ML, et al. Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 2001;19:389-97.
28. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;15:783-92.
29. Agus DB, Bunn PA Jr, Franklin W, Garcia M, Ozols RF. HER-2/neu as a therapeutic target in non-small cell lung cancer, prostate, and ovarian cancer. *Semin Oncol* 2000;27(6 Suppl 11):53-63.
30. Weiner LM, Adams GP, von Mehren M. Therapeutic monoclonal

- antibodies: general principles. In: De Vita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology*. Vol. 1, 6th edn. Philadelphia: Lippincott Williams & Wilkins, 2001:495–508.
31. Rosenberg SA. Progress in human tumour immunology and immunotherapy. *Nature* 2001;17:380–4.
 32. Warrell RP Jr. Differentiating agents. In: De Vita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology*. Vol. 1, 6th edn. Philadelphia: Lippincott Williams & Wilkins, 2001:489–94.
 33. Mauro MJ, O'Dwyer M, Heinrich MC, Druker BJ. STI571: a paradigm of new agents for cancer therapeutics. *J Clin Oncol* 2002;20:325–34.
 34. Goss PE, Strasser K. Aromatase inhibitors in the treatment and prevention of breast cancer. *J Clin Oncol* 2001;19:881–94.
 35. Nabholz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *J Clin Oncol* 2000;18:3758–67.
 36. Mouridsen H, Gershanovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the international letrozole breast cancer group. *J Clin Oncol* 2001;19:2596–606.
 37. Carroll PR, Lee KL, Fuks ZY, Kantoff PW. Cancer of the prostate. In: De Vita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology*. Vol. 1, 6th edn. Philadelphia: Lippincott Williams & Wilkins, 2001:1418–79.
 38. Boccardo F, Rubagotti A, Barichello M, et al. Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer patients: results of an Italian Prostate Cancer Project study. *J Clin Oncol* 1999;17:2027–38.
 39. Margolin K, Gordon MS, Holmgren E, et al. Phase Ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: pharmacologic and long-term safety data. *J Clin Oncol* 2000;18:851–6.
 40. Nelson AR, Fingleton B, Rothenberg ML, Matrisian LM. Matrix metalloproteinases: biologic activity and clinical implications. *J Clin Oncol* 2000;18:1135–49.

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Wealth and poverty: the one is the parent of luxury and indolence, and the other of meanness and viciousness, and both of discontent.

Plato, fourth century Greek philosopher

Capsule

Blocking malarial entry

The widespread resistance of the human malaria parasite *Plasmodium falciparum* to the few effective antimalarial drugs has led to a search for new therapeutic targets. Greenbaum et al. used a chemical proteomics screen to identify a cysteine protease, falcipain-1, that is essential for the parasite merozoites

to invade human red blood cells. By screening chemical libraries, the authors identified inhibitors that specifically blocked only falcipain-1 activity and parasite invasion of erythrocytes, but not other cysteine proteases or other stages in the parasite life cycle.

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Capsule

Occupational driving and lumbar disk degeneration

Back problems are reported more by occupational drivers than by any other occupational group. One explanation is that whole-body vibration caused by the vehicle leads to accelerated disk degeneration, herniation, and associated symptoms. Battie et al. investigated the effects of lifetime driving exposure on lumbar disk degeneration in monozygotic twins with very different histories of occupational driving during their life. They assessed 45 male monozygotic twin pairs from the population-based Finnish Twin Cohort, who had very different patterns of occupational driving during their lives. Data were obtained for

driving exposures and potential confounding factors through an extensive structured interview. Assessing disk degeneration with lumbar MRI, the authors found no difference in disk degeneration between occupational drivers and their twin brothers. They were unable to identify any overall tendency for greater degeneration or pathology in occupational drivers as compared to their twin brothers. Although driving may exacerbate symptoms of back problems, it does not damage the disk.

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