



Update on Targeted Therapy for Cancer

Dr. Godfrey CF Chan DMD, MD, LMCHK, MSc, FHKAM, FHKCPaed, FRCP(Edin), FRCPC(HK), FAAP
Clinical Associate Professor, Department of Paediatrics & Adolescent Medicine, the University of Hong Kong



Dr. Godfrey CF Chan

Traditionally, surgery, radiation therapy and chemotherapy are the 3 main forms of treatment modality for cancer. With the advances in these approaches, phenomenal progresses in the cure rate of many types of cancer have been achieved over the past 2 decades. However, even with this encouraging progress, many types of cancer remain incurable. In addition, there are limitations in all these approaches. Just to name a few examples, the resectability of surgery is dependent on the location of the tumour, also the extent of the tumour and its vascular infiltration. The feasibility of conventional radiation therapy is affected by the differences in sensitivity between the tumour cells and normal tissues, and in some situation, the location of the tumour (i.e. liver). Furthermore, both surgery and radiation therapy are local form of treatment that can lead to injury of the adjacent normal tissue and local treatment cannot get rid of the dispersed malignant tumour cells either at diagnosis or upon relapse.

The limitation for chemotherapy is that it may not be able to eradicate cancer with a big tumour bulk when it is used alone (exceptions are high grade lymphoma or germ cell tumour). Similar to radiation therapy, the response to chemotherapy is affected by the variable sensitivity of different cancers. While chemotherapy is a systemic therapy which can eradicate micro-metastase and small residual tumour cells, it also exerts more systemic toxicity. The anti-cancer effect of most chemotherapy is based on the fact that cancer cells grow faster than normal cells. Therefore, rapidly dividing cells are the "target" of the chemotherapeutic agents. The disadvantage of such non-specific approach is that normal tissues with high proliferating rate (such as mucosa, hair follicles & marrow hematopoietic cells) will be struck by the chemotherapeutic agents as well. This leads to the commonly encountered toxicity such as mucositis, hair loss and myelosuppression. In addition, many malignant tumour consist of heterogeneous cellular fractions in which some cancer cells have a slow proliferating rate (i.e. cancer stem cell). These slow dividing fractions are resistant to the conventional chemotherapy and will lead to relapse despite good initial response.

Targeted cancer therapy refers to therapy which attacks cancer cells in a specific and precise manner. That also means the cytotoxic effect on normal cells will be less. In general, there are two main types of targeted cancer therapy. One group can identify a particular extracellular marker (antigen) through a specific antibody (targeted immunotherapy). The antibody then induces cell lysis either through subsequent immune reaction (i.e. complement activation) or it exerts cytotoxic effect through additional conjugated radioactive or chemical components. Using either stimulated dendritic cells or activated T cells in the form of tumour vaccine is a different form of immunotherapy. Another group of agents make use of small molecules that block or inhibit a particular intracellular process from functioning (molecular targeted therapy). With increased understanding of the receptors and genes involved

in the signal transduction pathways of oncogenic proliferation, this approach gains some impressive success in recent years.

Targeted Immunotherapy by Monoclonal Antibody

The concept of immunotherapy using antibody to target at cancer cells is based on the hypothesis that human cancers express specific tumour-associated antigens (TAA) that can be specifically targeted by either antibody or cell mediated immunity. Hindrance in the past was partly due to the poor expression of TAA on the cellular surface or failure to identify unique TAA in many cancer cells. In addition, the production of specific antibodies for clinical use is a tedious and expansive process. Breakthrough in recent years was attributed by gaining more abundant information in identifying more TAA on different cancer cells and also the advance in the high through-put technology in generating massive amount of antibodies for clinical use. By attaching either radioactive substance such as Iode131, Yttrium 90 or cytotoxic conjugates to the antibody further enhance the anti-cancer potential in some of these antibodies.

MabThera is a chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes¹. The Fab domain of MabThera binds to the CD20 antigen on B lymphoid cells, and the Fc domain recruits immune cytolytic mechanism such as complement-dependent cytotoxicity and antibody-dependent cell mediated cytotoxicity². When it is given at a dose of 375mg/m² weekly for 4 courses, the mean serum half-life was 76 hours after the first infusion and 205 hours after the 4th dose³. Normal B-cell recovery began at 6 months following completion of treatment and returned to normal by 12 months. MabThera clinical trials on B-lineage non-Hodgkin lymphoma (NHL) included initial treatment of bulky disease and retreatment. Data from phase I and II trials confirmed its safety and efficacy. MabThera is active in indolent lymphoma such as follicular lymphoma, with an objective response rate varying from 48% to 73%. MabThera with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy increases the remission rate of high grade lymphoma such as diffuse large cells lymphomas (DLBCL) by approximately 15% (63% vs 76%) and also with better survival⁴. Recent systemic reviews confirmed the cost-effectiveness of MabThera/CHOP compared with CHOP alone for older patients (>60 years) with DLBCL^{5,6}. However, such clinical benefit in younger patients (18-59 years) was not as significant. MabThera is the first monoclonal antibody approved by the US Food and Drug Administration (FDA) for the treatment of cancer.

There are other on trial monoclonal antibody targeted at B lymphoid markers including Epratuzumab⁷; Campath and preliminary data have been encouraging⁸⁻¹¹ (Table 1). Using





the anti-CD20 antibody with radioactive conjugate had also been applied to patients who were refractory with the MabThera alone and yielded encouraging results. These included Zevalin¹² and Bexxar¹³. Oncolym is a monoclonal

antibody with radioactive conjugate targeted at HLA-DR10 protein¹⁴. This antigen is found in 80% of B-lymphoma cells but only 2% of normal B cells express HLA-DR10.

Name (other names)	Target	Tissue type	Current indication	Distributor
MabThera (Rituxan, Rituximab)	Anti-CD20	B lymphoid cells	NHL, PTL, CLL	Roche
Epratuzumab	Anti-CD22	B lymphoid cells	NHL	Immunomedics/Amgen
Campath-1H (Alemtuzumab)	Anti-CD52	B & T lymphoid cells, NK cells, monocytes, macrophages, male reproductive tissue	NHL, CLL	Berlex
Zevalin (⁹⁰ Yttrium ibritumomab tiuxetan)	Anti-CD20	B lymphoid cells	NHL	MDS Nordion
Bexxar (tositumomab and iodine ¹³¹ I)	Anti-CD20	B lymphoid cells	NHL	Corixa Corp
Oncolym (¹³¹ I Lym-1)	Anti-HLA-DR10	B lymphoid cells	NHL	Peregrine Pharmaceuticals
Mylotarg (CMA-676, Gemtuzumab ozogamicin)	Anti-CD33	Myeloid cells	AML	Wyeth
Herceptin (Trastuzumab)	Anti-HER2	Cancer cells overexpressing HER2 receptor	Breast cancer	Genetech / Roche
Erbix (Cetuximab)	Anti-EGFR	Cancer cells with aberrant EGFR	NSCLC, colorectal CA	Bristol-Myers Squibb
3F8	Anti-GD2	Neuroblastoma cells & afferent nerve	Neuroblastoma	MSKCC
Glivec (Gleevec, STI571, Imatinib)	BCR/Abl	Ph+ CML, c-Kit mutated tumours	CML, GIST	Novartis
Iressa (Gefitinib, ZD1839)	Epidermal growth factor receptor (EGFR)	Tumours with aberrant erbB family of tyrosine kinase receptors	Advanced non-small cell lung cancer	Astra-Zeneca
Tarceva (Erlotinib, OSI 774)	Epidermal growth factor receptor (EGFR)	Tumours with aberrant erbB family of tyrosine kinase receptors	Advanced non-small cell lung cancer	Genetech

Table 1: Selected monoclonal anti-cancer antibodies and molecular targeted anticancer agents

For non-lymphoid haemic malignancy, a monoclonal antibody known as Mylotarg is designed for the treatment of acute myeloid leukaemia (AML). Mylotarg binds specifically to the CD33 antigen, a glycoprotein commonly expressed by myeloid leukaemic cells. Mylotarg is a recombinant humanized antibody linked with a potent anti-tumour antibiotic called calicheamicin (a potent toxin). Pharmacokinetic study showed after a 9 mg/m² dose, the peak plasma concentration was 2.86 mg/L with a half life of 72 hours¹⁵. The concentration profiles of calicheamicin followed the same time course. In a phase II study of Mylotarg, it was found that within 3 to 6 hours after infusion, near complete saturation of CD33 antigenic sites by Mylotarg was reached for AML blasts¹⁶. After binding to CD33 antigen, Mylotarg was rapidly internalized and induced dose-dependent apoptosis in myeloid cells. The feasibility of combining Mylotarg with intensive chemotherapy (MRC-AML regimen) as first-line treatment of AML was assessed (aged 17 to 59 years)¹⁷. Sixty-four patients received induction chemotherapy with Mylotarg, remission was achieved in 86% of patients and 78% were still in continuous complete remission at 8 months. Mylotarg given with induction and consolidation was well tolerated. Similar approach was used for elderly patients (aged 61-75 years) with AML. Patients received frontline treatment with Mylotarg following by conventional chemotherapy (mitoxantrone, cytarabine, etoposide). The overall response rate to the entire induction sequence was 54.4%, with complete remission in 35.1% and complete remission with incomplete platelet recovery in 19.3%¹⁸. Rates of failure due to treatment-related mortality or resistant disease were 14.1% and 29.9%, respectively. Mylotarg has been approved by the FDA for the treatment of older patients in first relapse with CD33-positive acute myeloid leukemia (AML) since 1999. Its on younger patients with relapsed AML is currently under study¹⁹.

For non-haemic malignancy, an example is Herceptin. It is a monoclonal antibody targeted at a surface expressed antigen that is unique to a subset of breast cancer cells. Herceptin binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER2) then leads to cell lysis^{20, 21}. Amplification of the HER2 gene results in HER2 protein overexpression in approximately 25 to 30% of primary breast cancer patients²¹. Testing for HER2 has become an important marker in the management of breast cancer over the past few years. The pharmacokinetics of Herceptin showed short intravenous infusions once weekly demonstrated a dose-dependent pharmacokinetic with half-life averaged 1.7 and 12 days at the 100 and 500 mg dose levels respectively²². In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range= 1 to 32 days) was observed. A multicentre, randomized, controlled clinical trial has been conducted on 469 patients with metastatic breast cancer not previously treated²³. Patients were randomized to receive chemotherapy alone or in combination with Herceptin. Compared to chemotherapy alone, patients randomized to Herceptin plus chemotherapy arm experienced a significantly longer median time to disease progression, a higher overall response rate, a longer median duration of response, and a longer median survival. These treatment effects were observed both in patients who received Herceptin plus paclitaxel and Herceptin plus adriamycin/cyclophosphamide but the effects was greater in the Herceptin plus paclitaxel subgroup. Herceptin received FDA approval in 1998 for use in women with metastatic breast cancer who have tumors that overexpress the HER2 protein. It is currently being studied in clinical trials for other types of cancer with HER2 protein overexpressed, including osteosarcoma and cancers of the lung, pancreas, salivary gland, colon, prostate, endometrium, and bladder.



Other anti-EGFR monoclonal antibody includes Erbitux²⁴. In addition, antibody targeted at different mechanisms or antigens includes: 1) anti-angiogenesis (anti-VEGF) such as Avastin and PTK/ZK for the treatment of colorectal cancer²⁵; 2) anti-ganglioside-2 such as ch14.18²⁶ and 3F8²⁷ for the treatment of neuroblastoma.

Targeted Molecular Therapy

In recent years, due to the drastic increase in the knowledge on the genetic events involved in the pathogenesis, proliferation and metastasis of cancers, specifically designed agents which can block a defined step in some of these key events became available. Some of the currently FDA approved agents include Glivec, Iressa and Tarceva.

Glivec is small molecule inhibitor on specific enzymes (Bcr/Abl) aberrantly found in Chronic Myeloid Leukaemia (CML) that causes uncontrolled growth of the leukocytes. Glivec completely shuts down Bcr/Abl leading to arrest of cell growth and death. In addition, it also inhibits the stem-cell factor receptor (c-kit) and platelet-derived growth factor receptor (PDGF)²⁸. The c-kit tyrosine kinases are activated by mutation in the majority of patients with a rare intestinal cancer called gastrointestinal stromal tumours (GIST)²⁹ and in a variety of other solid tumours as well. However, the blood brain barrier seems to prevent the use of Glivec in brain tumours³⁰.

A phase I trial showed patients received Glivec orally with the dose range of 350 mg/day achieved a mean plasma trough concentration of approximately 1 mmol/L 24 hours after administration. This exceeds the 50% inhibitory concentration required to inhibit proliferation of Bcr/Abl-positive leukemia cells³¹. The effectiveness of Glivec on CML based on haematological response (HR) and cytogenetic response (CR) rates has been evaluated in several clinical trials. In patients who were newly diagnosed with CML in early chronic phase, Glivec 400 mg/day compared with interferon-alpha (IFN α) plus cytarabine resulted in higher HR and CR rates and fewer patients progressing to the accelerated phase or blast crisis in a large comparative trial. Preliminary results indicate that compared with IFN α plus cytarabine, Glivec treatment was associated with similar total costs, but resulted in a higher health-related quality of life (HR-QOL)³². However, the duration of response in this category is not yet defined³³. In patients with Ph+ CML in late chronic phase who failed conventional therapy, current trials showed around 88% of patients could maintain their cytogenetic response up to 2 years with Glivec. And in patients with Ph+ CML in accelerated phase, around 64% of patients could maintain their cytogenetic response up to 2 years. Finally, in patients with Ph+ CML in blast crisis, around 27% of patients could maintain their hematological response up to 2 years³⁴. FDA currently approved Glivec for treating patients with CML in myeloid blast crisis, CML in accelerated phase, or CML in chronic phase after failure of interferon treatment.

Iressa is a compound that selectively and reversibly blocks the activity of ectodermal growth factor receptor (EGFR) by competitively inhibiting the binding of adenosine triphosphate, which is required for receptor autophosphorylation and kinase activation. In a phase I trial, a single oral dose of Iressa (dose escalation from 50 mg/day to a maximum of 925 mg/day) followed by 10-14 days rest period, two of six patients at 700 mg/day developed dose-limiting toxicity. Maximum serum concentration was reached within 3-7 hours and exposure to Iressa increased with dose. Mean half-life following multiple dosing was 50 hours³⁵. In a

multicentre randomized Phase II trial using Iressa as 2nd or 3rd line single-agent therapy, 210 patients with non-small cell lung carcinoma (NSCLC) of unselected EGFR expression status were recruited. They received either 250 or 500 mg oral Iressa daily⁽³⁶⁾. Similar overall response rates of around 18-19% and disease stabilization rates of 32-36% were noted. The Median progression-free survival duration was 2.8 months. A parallel randomized Phase II study (IDEAL 2)³⁷ involved 216 unselected symptomatic patients with advanced refractory NSCLC, improvement in symptoms was observed in 43% of all patients. The 1-year overall survival rate for patients in the IDEAL 2 trial was 25% but the higher Iressa dose (500 mg) was found to be associated with more severe side effects, such as an acne-like skin rash and diarrhea.

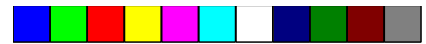
It is not known whether elderly patients' rates of response to Iressa therapy will be similar to that in younger patients. Recently, a subgroup of patients with NSCLC had specific mutations in the EGFR kinase domain showed higher clinical responsiveness to Iressa^{38, 39}. Thus, screening for specific mutations in lung malignancies may lead to the identification of patients who are more likely to respond to treatment. When Iressa was used in combination with chemotherapy, two large Phase III trials involving younger patients with NSCLC have reported that platinum-based chemotherapy plus Iressa does not yield any survival benefit compared with chemotherapy alone^{40, 41}. Iressa is approved by the FDA as a treatment for patients with NSCLC who failed to respond to platinum-based and taxel-based chemotherapy. Use of Iressa in other cancer types which have EGFR mutation such as breast, colorectal, head & neck, prostate, gastric, prostate and medulloblastoma are currently under investigation⁴². Another anti-EGFR known as Tarceva⁴³ has also been tested in NSCLC and other tumours currently.

In addition, new classes of molecular targeted agents currently under clinical investigations include histone deacetylase inhibitors (i.e. sodium n-butyrate, suberoylanilide hydroxamic acid, LAQ824, CI-994, MS-275, and depsipeptide) for treating AML and lung cancer⁴⁴. The histone deacetylase inhibitors have been shown to induce differentiation, decrease cell proliferation, and induce cell death in pre-clinical settings. The other class is farnesyl transferase inhibitor (i.e. R115777, tipifarnib, Zarnestra) that blocks the farnesylation of cytoplasmic RAS (inactive) oncogene to membrane RAS (active). RAS has been found to be an important molecule involved in the signal transduction pathways for cell proliferation and survival in many cancers⁴⁵. Many other molecular approaches have been under intense investigations in the pre-clinical stage at the moment.

Side Effects of targeted therapy

Even the toxicity of targeted therapy are in general less than that of conventional treatment modalities, they are not free of side effects. For antibody immunotherapy, the side effects are mainly related to the anaphylactic reaction (less common in humanized product); infusion reaction (fever, chills and rigors) and the effects related to the shared common normal targets that the antibody attacked. For example, B lymphopenia and hypogammaglobulinaemia is expected in MabThera treatment; neutropenia is expected in Mylotarg treatment. Due to the toxicity of the chemical conjugate, severe hepatic impairment in particularly in the form of veno-occlusive disease has been reported in Mylotarg treatment^{17, 46}. The most serious adverse reactions caused by Herceptin include cardiomyopathy, pulmonary events, and exacerbation of chemotherapy-induced neutropenia.





For targeted molecular therapy such as Glivec, most side effects were mild or moderate such as fluid retention, gastrointestinal upset such as nausea and vomiting, myalgia, fatigue and rash. Some of these side effects may be difficult to distinguish from the complications caused by the underlying disease. More severe side effects happened in less than 10% of patients but only around 4-5% of patients discontinued the drug due to side effect²⁸. For Iressa, most adverse events were mild (grade 1/2) and the most frequent ones were an acne-like rash and gastrointestinal effects³⁵.

Conclusion

As we understand more about the basic mechanisms of cancer growth and characteristics of cancer cells, increasing numbers of new novel agents with unique anti-cancer effect are expected to be discovered. However, due to the huge expenses spent in the research and clinical trials, in addition to the commercial profit required by many stock-holding pharmaceutical companies, the current products are all remarkably expensive. Furthermore, some of the targeted agents induce cytostatic rather than cytotoxic effect, meaning that prolonged use of the agents is required. The expenses on treatment of cancer are expected to be escalating rapidly. We envisioned that many of these targeted agents may not be able to benefit most patients in the developing countries due to their inhibitory high costs. Even in a more affluent society such as Hong Kong, facing with this fascinating yet challenging new era in medical care, our health care authorities have to deal with it in a prospective manner. Among them, setting up proper and transparent cost-effective analysis mechanism for new drugs and techniques; and adopting a feasible health care financing policy may be urgently needed.

References

- Hennesy BT, Hanrahan EO, Daly PA. Non-Hodgkin lymphoma: an update. *Lancet Oncol* 2004;5(6):341-53.
- Olszewski AJ, Grossbard ML. Empowering targeted therapy: lessons from rituximab. *Sci STKE* 2004;2004(241):pe30.
- Berinstein NL, Grillo-Lopez AJ, White CA, et al. Association of serum Rituximab (IDEC-C2B8) concentration and anti-tumor response in the treatment of recurrent low-grade or follicular non-Hodgkin's lymphoma. *Ann Oncol* 1998;9(9):995-1001.
- Mounier N, Gisselbrecht C. [Monoclonal antibodies in the treatment of lymphoma]. *Rev Prat* 2002;52(9):982-5.
- Knight C, Hind D, Brewer N, Abbott V. Rituximab (MabThera(R)) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation. *Health Technol Assess* 2004;8(37):1-96.
- Malliti M, Junot H, Fievet MH, et al. [Treatment of malignant non-Hodgkin's lymphoma. Economic impact of rituximab (Mabthera) versus conventional chemotherapy]. *Ann Med Interne (Paris)* 2003;154(3):139-47.
- Leonard JP, Coleman M, Ketas JC, et al. Phase I/II trial of epratuzumab (humanized anti-CD22 antibody) in indolent non-Hodgkin's lymphoma. *J Clin Oncol* 2003;21(16):3051-9.
- Uppenkamp M, Engert A, Diehl V, Bunjes D, Huhn D, Brittinger G. Monoclonal antibody therapy with CAMPATH-1H in patients with relapsed high- and low-grade non-Hodgkin's lymphomas: a multicenter phase I/II study. *Ann Hematol* 2002;81(1):26-32.
- Khorana A, Bunn P, McLaughlin P, Vose J, Stewart C, Czuczman MS. A phase II multicenter study of CAMPATH-1H antibody in previously treated patients with nonbulky non-Hodgkin's lymphoma. *Leuk Lymphoma* 2001;41(1-2):77-87.
- Lundin J, Osterborg A, Brittinger G, et al. CAMPATH-1H monoclonal antibody in therapy for previously treated low-grade non-Hodgkin's lymphomas: a phase II multicenter study. European Study Group of CAMPATH-1H Treatment in Low-Grade Non-Hodgkin's Lymphoma. *J Clin Oncol* 1998;16(10):3257-63.
- Tang SC, Hewitt K, Reis MD, Berinstein NL. Immunosuppressive toxicity of CAMPATH1H monoclonal antibody in the treatment of patients with recurrent low grade lymphoma. *Leuk Lymphoma* 1996;24(1-2):93-101.
- Gregory SA. Selecting patients for treatment with 90Y ibritumomab tiuxetan (Zevalin). *Semin Oncol* 2003;30(6 Suppl 17):17-22.
- Rajendran JG, Fisher DR, Gopal AK, Durack LD, Press OW, Eary JF. High-dose (131I)-tositumomab (anti-CD20) radioimmunotherapy for non-Hodgkin's lymphoma: adjusting radiation absorbed dose to actual organ volumes. *J Nucl Med* 2004;45(6):1059-64.
- DeNardo GL, DeNardo SJ, Lamborn KR, et al. Low-dose, fractionated radioimmunotherapy for B-cell malignancies using 131I-Lym-1 antibody. *Cancer Biother Radiopharm* 1998;13(4):239-54.
- Dowell JA, Korth-Bradley J, Liu H, King SP, Berger MS. Pharmacokinetics of gemtuzumab ozogamicin, an antibody-targeted chemotherapy agent for the treatment of patients with acute myeloid leukemia in first relapse. *J Clin Pharmacol* 2001;41(11):1206-14.
- van Der Velden VH, te Marvelde JG, Hoogveen PG, et al. Targeting of the CD33-calicheamicin immunoconjugate Mylotarg (CMA-676) in acute myeloid leukemia: in vivo and in vitro saturation and internalization by leukemic and normal myeloid cells. *Blood* 2001;97(10):3197-204.
- Kell WJ, Burnett AK, Chopra R, et al. A feasibility study of simultaneous administration of gemtuzumab ozogamicin with intensive chemotherapy in induction and consolidation in younger patients with acute myeloid leukemia. *Blood* 2003;102(13):4277-83.
- Amadori S, Suci S, Willemze R, et al. Sequential administration of gemtuzumab ozogamicin and conventional chemotherapy as first line therapy in elderly patients with acute myeloid leukemia: a phase II study (AML-15) of the EORTC and GIMEMA leukemia groups. *Haematologica* 2004;89(8):950-6.
- Buckwalter M, Dowell JA, Korth-Bradley J, Gorovits B, Mayer PR. Pharmacokinetics of gemtuzumab ozogamicin as a single-agent treatment of pediatric patients with refractory or relapsed acute myeloid leukemia. *J Clin Pharmacol* 2004;44(8):873-80.
- Coussens L, Yang-Feng TL, Liao YC, et al. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. *Science* 1985;230(4730):1132-9.
- Press MF, Pike MC, Chazin VR, et al. Her-2/neu expression in node-negative breast cancer: direct tissue quantitation by computerized image analysis and association of overexpression with increased risk of recurrent disease. *Cancer Res* 1993;53(20):4960-70.
- Baselga J. Phase I and II clinical trials of trastuzumab. *Ann Oncol* 2001;12 Suppl 1: S49-55.
- 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;344(11):783-92.
- Damjanovic D, Thompson P, Findlay MP. Evidence-based update of chemotherapy options for metastatic colorectal cancer. *ANZ J Surg* 2004;74(9):781-7.
- Bilenker JH, Haller DG. Future directions with angiogenesis inhibitors in colorectal cancer. *Clin Colorectal Cancer* 2004;4 Suppl 2:S86-93.
- Simon T, Hero B, Faldum A, et al. Consolidation treatment with chimeric anti-GD2-antibody ch14.18 in children older than 1 year with metastatic neuroblastoma. *J Clin Oncol* 2004;22(17):3549-57.
- Cheung Y, Lo Piccolo MS, Kushner BH, Cheung NK. Early molecular response of marrow disease to biologic therapy is highly prognostic in neuroblastoma. *J Clin Oncol* 2003;21(20):3853-8.
- Hernandez-Boluda JC, Cervantes F. Imatinib mesylate (Gleevec, Glivec): a new therapy for chronic myeloid leukemia and other malignancies. *Drugs Today (Barc)* 2002;38(9):601-13.
- Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol* 2004;22(18):3813-25.
- Dai H, Marbach P, Lemaire M, Hayes M, Elmquist WF. Distribution of STI-571 to the brain is limited by P-glycoprotein-mediated efflux. *J Pharmacol Exp Ther* 2003; 304(3):1085-92.
- Peng B, Hayes M, Resta D, et al. Pharmacokinetics and pharmacodynamics of imatinib in a phase I trial with chronic myeloid leukemia patients. *J Clin Oncol* 2004;22(5):935-42.
- Curran MP, Groom KE, Goa KL. Spotlight on imatinib mesylate in chronic myeloid leukemia. *BioDrugs* 2004;18(3):207-10.
- Angstreich GR, Smith BD, Jones RJ. Treatment options for chronic myeloid leukemia: imatinib versus interferon versus allogeneic transplant. *Curr Opin Oncol* 2004;16(2):95-9.
- Melo JV, Hughes TP, Apperley JF. Chronic myeloid leukemia. *Hematology (Am Soc Hematol Educ Program)* 2003:132-52.
- Nakagawa K, Tamura T, Negoro S, et al. Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Japanese patients with solid malignant tumors. *Ann Oncol* 2003;14(6):922-30.
- Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003;21(12):2237-46.
- Herbst RS. Dose-comparative monotherapy trials of ZD1839 in previously treated non-small cell lung cancer patients. *Semin Oncol* 2003;30(1 Suppl 1):30-8.
- Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350(21):2129-39.
- Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304(5676):1497-500.
- Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial-INTACT 1. *J Clin Oncol* 2004;22(5):777-84.
- Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial-INTACT 2. *J Clin Oncol* 2004;22(5):785-94.
- Salomon DS, Brandt R, Ciardiello F, Normanno N. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol* 1995; 19(3):183-232.
- Perez-Soler R. The role of erlotinib (Tarceva, OSI 774) in the treatment of non-small cell lung cancer. *Clin Cancer Res* 2004;10(12 Pt 2):4238s-40s.
- Piekarr R, Bates S. A review of desipeptide and other histone deacetylase inhibitors in clinical trials. *Curr Pharm Des* 2004;10(19):2289-98.
- Russo P, Loprevite M, Cesario A, Ardizzoni A. Farnesylated proteins as anticancer drug targets: from laboratory to the clinic. *Curr Med Chem Anti-Canc Agents* 2004; 4(2):123-38.
- Giles FJ, Kantarjian HM, Kornblau SM, et al. Mylotarg (gemtuzumab ozogamicin) therapy is associated with hepatic venoocclusive disease in patients who have not received stem cell transplantation. *Cancer* 2001;92(2):406-13.