Targeted Chemotherapeutics: An Overview of the Recent Progress in Effectual Cancer Treatment

A. Kulhari, A. Sheorayan and A. Chaudhury
Department of Bio and Nano Technology, Bio and Nano Technology Centre, Guru Jambheshwar University of Science and Technology, Hisar-125 001 (Haryana), India

ABSTRACT
Background: Cancer is now becoming most prevalent human disease requiring early detection, prevention, diagnosis and effective cure. Defects in apoptotic signaling and up-regulation of drug transporters in cancer cells significantly limit the effectiveness of cancer chemotherapy. Complex signaling network involving multiple proteinks have made disease etiology even more challenging. Ability of cancer cells to avoid apoptosis and continued proliferation is one of the fundamental hallmarks, therefore, is a major target of anti-cancer therapy. Evaluation of chemotherapies and other novel therapeutic strategies for overcoming mechanisms of resistance and effective treatment via curing management is a mammoth task. Deep thought should be given not only for the assessment of safety and pre-examination of efficacy in versatile treatment approach, but also to contemplation towards community practice settings, patient expectations, compliance and cost effectiveness. Multivariate pre-clinical findings indicate the effectiveness of combined treatment regimes over single agent based first line therapies towards increasing survival rate of patients. Results: Comprehensive review of concerted efforts in designing chemotherapeutics through a combination of several drugs for various types of cancers by way of over a dozen treatment strategies ranging from molecular targeted gene therapy to radiotherapy has been presented. Conclusion: It is hoped that novel experimental therapies when applied instantaneously after early detection or rejection of primary therapy for prevention of cancer progression in a timely manner before turning fatal will be very useful. It is envisaged that constant search for enhanced immune-modulator drug formulations will definitely give fruitful results for combating serious threat of cancer in future.

Key words: Cancer, tumor, radiotherapy, monoclonal antibody, metastases, immunity

Pharmacologia 4 (9): 535-552, 2013

INTRODUCTION
In today’s life cancer becomes the most common cause of human mortality, especially its frequency raised in resource poor developing countries which are trying to improve their GDP and started to catch up western world lifestyles. Researchers, clinicians and traditional holistic approaches are perplexed in understanding the natural history and unpredictable outcome of cancer despite applying various complementary, alternative, non-conventional therapies which are based on immune-boost up, surgery, heating therapies, chemo, metabolic, pharmacological, behavioural, psychological, biological, herbal and nutritional aspects with variable extrapolative factors and manifestation in individual and composite evaluation (Retsky et al., 2012). However, there are more than 20 different types of cancers which afflict human system (Chen and Pauline, 2011) Fig. 1. Only 15% patients suffering with lung cancer have shown 5-year survival (in USA), whereas, in developing countries the survival rate does not exceed more than 8.9% (Parkin et al., 2005). From last 30 years clinicians are trying to resolve the mystery of causing elements and biology of cancer. Conventional therapy for curing cancer are surgery, radiotherapy, chemotherapy, adjuvant chemotherapy, endocrine therapy, anti-hormonal treatment, however, many of them showed depressing results and patients often succumb without an effective healing Fig. 1 (Benson et al., 2009). A combination of regimen has been found to be a better clinical asset and improved progression-free-survival and overall survival as compared to single chemotherapeutic treatment (O’Shaughnessy et al., 2011). Preference for different therapies has been based on baseline tumor characteristics such as size of tumor, estrogen receptor (ER), progesterone-receptor (PR) and human epidermal growth factor receptor-2 (HER’s-2), involvement of lymph node and sensitivity and resistance of tumors.
against different drugs (Bayraktar and Gluck, 2012). Currently various therapeutic strategies for treating cancer via blockade of cell signalling includes growth factor signalling (epidermal growth factor, vascular endothelial growth factor, platelet-derived growth factor receptor, human epidermal growth factor receptor-2, hepatocyte growth factor, fibroblast growth factor). Signalling adapter (Tumor necrosis factor-6), prostaglandin production (COX-2), inflammation (inflammatory cytokines: NF-kB, TNF, IL-1, IL-6, chemokines), cell cycle proteins (cyclin D1 and cyclin E), invasion (matrix metalloproteinases). Anti-apoptosis (bcl-2, bcl-XL, XIAP, survivin, FLIP), cellular proliferation (c-myc, AP-1, growth factors), drug resistance gene products (multi-drug resistance) are also targeted Fig. 1 and Table 1 (Aggarwai et al., 2006). Still there is no ultimate finale, describing best treatment or any therapeutic strategy and standard analytical features for saving the lives of multiple cancer carriers in world. Maximum evidences based on various therapeutic regimens are insufficient for recommendation of a particular drug or therapy as a standard treatment in spite of diverse potential trials in in vivo or in vitro. According to a recent report published in News Magazine “The Atlantic” the expenses for treatment of cancer patients by chemotherapy in United States of America is nearly US$ 70,000, whereas, in India it merely costs US$ 2,500. Another good example of Gleevec (imatinib) drug marketed by Novartis AG for treatment of blood cancer was recently not awarded Patent in India because the drug manufactured by Novartis AG costs more than US$ 2100, whereas, the Indian variant which is quite similar to Gleevec is available merely for US$ 140. The aim of this review is to explore and document significant information regarding various synthetic therapeutic regimens which are currently used to accelerate the treatment of this deadly disease: Cancer.

**Gallbladder (GBC) and pancreatic cancer:** GBC is a rare disease of the hepatobiliary tract and is difficult to diagnose due to very poor clinical presentation and survival depends on remedial resection according to stage of disease (Shukla et al., 1985; Zatorski et al., 1992). External radiotherapy after resectional surgery has shown some survival benefits, although it also affects normal cells and up to some extent it is relatively radio-resistant. In some case a combination of mitomycin C with or without systemic 5FU has found some increased survival, rates, although further investigation is required for recommendation of radiotherapy in patients with carcinoma gallbladder either as an adjuvant or as a palliative curative approach (Smith et al., 1984;
<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Management</th>
<th>Side effects</th>
<th>Notes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td><strong>Surgery</strong></td>
<td>Infection, wound complications and lymphedema</td>
<td>Current standard of care for patients with a positive sentinel lymph node</td>
<td>Hardin and Lange (2012)</td>
</tr>
<tr>
<td>Metastatic melanoma</td>
<td>Vemurafenib used as targeted therapies against serine-threonine kinase and <strong>Immunotherapy</strong></td>
<td>Vemurafenib is arthralgias, rash, fatigue, peripheral facial palsy and a difficult to overemphasize photosensitivity</td>
<td>Vemurafenib was found significantly efficient by showing 50-70% response rate in advanced disease by targeting serine-threonine kinase, whereas imatinib immunotherapy displayed enhanced survival and durable tumor regression. Overall survival have never determined and very little number of patients are treated due to unavailability of expertise management regarding IL-2-related toxicities.</td>
<td>Curti and Urba (2012)</td>
</tr>
<tr>
<td>Metastatic melanoma</td>
<td><strong>Synthetic drug and cytokinins</strong></td>
<td>High - dose IL-2 caused hypotension and severe organ dysfunction</td>
<td>Conferred more survival benefit as compared to surgery or radiation alone in selected patients.</td>
<td>Curti and Urba (2012)</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>Combination of SRS and whole brain radiation therapy (WBRT)</td>
<td>Utilized multiple cobalt sources and radiation</td>
<td>Associated with long-term toxicities in WBRT with long-term survival</td>
<td>Williams et al. (2012)</td>
</tr>
<tr>
<td>Grade IV glioblastoma</td>
<td>Radiotherapy plus concomitant and adjuvant temozolomide (RTCA)</td>
<td>Imidazotetrazine derivative of the allylating agent dacarbazine</td>
<td>Nausea, vomiting, thrombocytopenia and leukopenia</td>
<td>Williams et al. (2012)</td>
</tr>
<tr>
<td>Metastatic colorectal cancer; Secondary CNS malignancies</td>
<td>Bevacizumab (humanized MAb)</td>
<td>Significant increase in the risk of bleeding and adversely affect the wound-healing process, along with its slow clearance and long elimination half-life in body; Increased threat of venous thromboembolism (VTE)</td>
<td>Quite effective in phase II trial in adenocarcinoma of the esophagus</td>
<td>Kelsen et al. (2006), Shah et al. (2006) and Yildiz et al. (2012)</td>
</tr>
<tr>
<td>Cancers of the esophagus and gastroesophageal junction</td>
<td>Surgically unresectable associated with bevacizumab (against VEGF), capcitabine, irinotecan, docetaxel and 5-FU</td>
<td>Surgery combined with synthetic drug</td>
<td>Higher dose of Bevacizumab can cause adverse events viz., bleeding, hypertension, thromboembolism, fistulization and perforation were rate</td>
<td>Quite effective with high efficacy and tolerable</td>
</tr>
<tr>
<td>Metastatic colorectal cancer</td>
<td>Bevacizumab in combination with biweekly FOLFOXIRI regimen</td>
<td>Bevacizumab (humanized MAb) and FOLFIRI regimen is a chemotherapy treatment (folinic acid, 5-FU, irinotecan)</td>
<td>Bleeding, hypertension, thromboembolism, fistulization and perforation were rate</td>
<td>Quite effective with high efficacy and tolerable</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Radioembolization</td>
<td>Utilization of percutaneous transarterial techniques for injecting radioisotope loaded micron-sized embolic particles</td>
<td>No life-threatening or fatal toxicities</td>
<td>Revealed 408 days median survival and 81% maintained stable disease. higher dose was found to be effective in terms of greater tumor response and increased survival</td>
</tr>
<tr>
<td>Metastatic colorectal cancer</td>
<td>Regorafenib (an oral tyrosine kinase inhibitor)</td>
<td>Target multiple receptors viz., VEGFR1-3, PDGFR beta, FGFR1 and KIT</td>
<td>Hand-foot skin reactions and hypertension</td>
<td>Found to be effective against third line metastatic colorectal cancer and showing longest progression free rate in gastrointestinal stromal tumors than any other tested drug in a phase III study</td>
</tr>
<tr>
<td>GIST</td>
<td>Nilotinib ascertain for which inhibits BCR-ABL, KIT and PDGFRs</td>
<td>Fatigue and gastrointestinal complaints</td>
<td>Following drug contain promising activity in imatinib and sunitinib resistant GIST in a phase I study</td>
<td>Mazumdar et al. (2009)</td>
</tr>
<tr>
<td>Type of cancer</td>
<td>Treatment</td>
<td>Drug/Therapy Description</td>
<td>Side Effects/Compliance/Outcomes</td>
<td>Reference(s)</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>FOLFOX chemotherapy with bevacizumab</td>
<td>Bevacizumab (humanized monoclonal antibody against VEGF)</td>
<td>Common side effects associated with bevacizumab are: Bleeding, hypertension, thromboembolism, fistulization and perforation</td>
<td>Tagawa and Bartness (2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cetuximab (partially humanised murine Mab and radiation sensitizer)</td>
<td>Cetuximab are acne like rashes, photosensitivity, hypomagnesemia and less commonly pulmonary and cardiac toxicity</td>
<td>Pinto et al. (2009) and Chan et al. (2011)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Cetuximab combined with doublet chemotherapy and three discrete chemotherapy</td>
<td>Cetuximab (partially humanised murine Mab and radiation sensitizer)</td>
<td>Shows minimal activity as a single agent, whereas its combination with doublet chemotherapy and three discrete chemotherapy backbones presented significant increase in response rate and median overall survival (5%, 3.1 months), (41.63%, 9.16 m) and more than 50%, respectively.</td>
<td></td>
</tr>
<tr>
<td>Metastatic gastrointestinal stromal tumours</td>
<td>Targeted therapy with imatinib</td>
<td>Imatinib (inhibitor of receptor tyrosine kinase enzyme)</td>
<td>Common side effects are weight gain, reduced number of blood cells (neutropenia, thrombocytopenia, anemia), headache, edema, nausea, rash and muscular skeletal pain</td>
<td>Chan et al. (2012)</td>
</tr>
<tr>
<td>Sporadic1 gastrointestinal stromal tumours</td>
<td>Adjuvant therapy with imatinib</td>
<td>Imatinib (inhibitor of receptor tyrosine kinase enzyme)</td>
<td>Common side effects are weight gain, reduced number of blood cells (neutropenia, thrombocytopenia, anemia), headache, edema, nausea, rash and muscular skeletal pain</td>
<td>Chan et al. (2012)</td>
</tr>
<tr>
<td>Advanced renal cell carcinoma and gastrointestinal stromal tumors</td>
<td>Sunsitib malate with immunomodulatory drug faginolod</td>
<td>Sunsitib malate is a multiligated receptor tyrosine kinase inhibitor and faginolod is a sphingosine-1-phosphate analog</td>
<td>Generally some side effects are associated with sunsitib therapy are fatigue, diarrhea, nausea, anorexia, hypertension, a yellow skin discolouration, hand-foot skin reaction, and stomatitis, although. This dual therapy did not exhibit any cumulative toxicity</td>
<td>Mousseau et al. (2012)</td>
</tr>
<tr>
<td>Leptomeningeal metastases</td>
<td>Capecitabine</td>
<td>Capecitabine (an oral prodrug and an antimetabolite of cell division inhibitor)</td>
<td>General side effects of Capecitabine are acne like rashes photosensitivity, hypomagnesemia and less commonly pulmonary and cardiac toxicity</td>
<td>Paydas et al. (2009)</td>
</tr>
<tr>
<td>Aflatinib</td>
<td>Irreversible EGFR inhibitor</td>
<td>Aflatinib can causes rash, diarrhoea and elevations in transaminases</td>
<td>Found effective in brain metastases from NSCLC, whereas combination strategy in gefitinib or erlotinib resistant tumors had a shown &gt;90% overall response rate systemically</td>
<td>Yap et al. (2010) and Janjigian et al. (2011)</td>
</tr>
<tr>
<td>Type of cancer</td>
<td>Therapy/Agent</td>
<td>Side Effects/Pharmacokinetics</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Liquid tumors and</td>
<td>Mafosfamide, Cyclophosphamide-like alkylating agent</td>
<td>Drug is under investigation as a chemotherapeutic and several phase I trials have been completed</td>
<td>Blaney et al. (2008)</td>
<td></td>
</tr>
<tr>
<td>primary brain tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>Soralenb therapy in combination with locoregional therapy</td>
<td>Skin rash, hand-foot skin reactions, diarrhea and hypertension</td>
<td>Vageli and Hirose (2013)</td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>Combination of HIF-1 inhibitor and β-enamele</td>
<td>Innovative drug, with fewer side effects</td>
<td>Li et al. (2011) and Liang et al. (2012)</td>
<td></td>
</tr>
<tr>
<td>HER-2 positive</td>
<td>Primary chemotherapy containing trastuzumab in combination with paclitaxel and FEC-75</td>
<td>Hematologic toxicity, neutropenia, febrile neutropenia, ischemic stroke, pulmonary embolism, atrial fibrillation. Although, some were successfully treated</td>
<td>Verma and Clemons (2007) and Telli and Ford (2010)</td>
<td></td>
</tr>
<tr>
<td>breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic breast cancer</td>
<td>Lapatinib and pertuzumab associated with trastuzumab</td>
<td>There are no changes in cardiac toxic effects</td>
<td>Urch et al. (2010), Dinera et al. (2012) and Gianni et al. (2017)</td>
<td></td>
</tr>
<tr>
<td>BRCA1-Deficient</td>
<td>Poly ADP-ribose polymerase and platinum salts</td>
<td>Generally platinum based monotherapy are with toxicity and poor oral bioavailability</td>
<td>Kennedy et al. (2004) and Byrd et al. (2010)</td>
<td></td>
</tr>
<tr>
<td>breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple-negative</td>
<td>Platinum associated with Cetuximab</td>
<td>General side effects of Cetuximab are acne-like rash, photosensitivity, hypomagnesemia and less commonly pulmonary and cardiac toxicity</td>
<td>Carey et al. (2007)</td>
<td></td>
</tr>
<tr>
<td>breast cancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen or aromatase inhibitors</td>
<td>Tamoxifen (anti-estrogenic)</td>
<td>Main side effects are bone loss, thromboembolism, reduced cognition</td>
<td>Telli and Ford (2010) and Girgert et al. (2012)</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Adjutant tamoxifen</td>
<td>Some treatment toxicity (osteoporosis and joint disorders such as arthritis, arthrosis and arthralgia) was exerted on survival with both the treatments</td>
<td>Kanapuru et al. (2012)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aromatase inhibitors have proven more beneficial than tamoxifen fewer side effects in post menopausal breast cancer women.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of cancer</td>
<td>Drug</td>
<td>Mode of action</td>
<td>Side effects</td>
<td>Drug effects</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ER-positive breast cancer</td>
<td>Arzoxifene (selective estrogen receptor modulators (SERMs))</td>
<td>Some side effects viz: venous thromboembolism, vasomotor symptoms, muscle cramps, and some gynecological events were found with arzoxifene treatment</td>
<td>Selective estrogen receptor modulators (SERMs) and arzoxifene found to be effective in reducing the frequency of invasive ER-positive breast cancer in postmenopausal women with low bone mass or osteoporotic, although detailed clinical research is required for development of the drug in future</td>
<td>Powles et al. (2012)</td>
</tr>
<tr>
<td>Advanced renal cell cancer</td>
<td>Pazopanib (synthetic indolopyrimidine)</td>
<td>Targets multiple kinases, viz., VEGFR1-3 and PDGFR</td>
<td>Fatigue, diarrhea, nausea, weight loss and hypertension</td>
<td>The drug has shown 12 weeks progression-free rate in leiomyosarcoma (44%), synovial sarcoma (39%), liposarcoma (26 %) and other types of STS (39%) in stratified phase 2 clinical trial, showed 97% disease control rate and 41.3 months progression-free survival (PFS) in first line phase II study. Intralymphatic delivery induces higher drug concentrations in the retroperitoneal lymph nodes when compared with intravenous administration</td>
</tr>
<tr>
<td>Metastatic GIST</td>
<td>Masitinib</td>
<td>An oral tyrosine kinase inhibitor</td>
<td>Rash, asthenia, diarrhea, nausea and muscle cramps</td>
<td></td>
</tr>
<tr>
<td>Breast, lung, head, neck and ovary cancer</td>
<td>Cisplatinum, carboplatinum and oxaliplatin</td>
<td>Platinum-based chemotherapeutics</td>
<td>Renal toxicity, hypertension, anemia, reduced fertility and acute leukemia</td>
<td>Zor et al. (2012)</td>
</tr>
</tbody>
</table>
Houaty et al., 1989). For pancreatic cancer currently most effective anticancer drug gemcitabine is used as a palliative chemotherapy but it rarely met the clinically satisfactory responses. To overcome the drug resistance problem of pancreatic cancer a novel agent triptolide (TPL) has been examined and it exert anti-tumor activity through induction of a strong inhibition of tumor growth activity equivalent to gemcitabine through down-regulation of DcR3 (Regulator of Fas ligand mediated apoptosis signalling) expression and apoptosis associated immunosuppressive activities (Wang et al., 2012).

**Melanoma:** Higher expression levels of immunomodulatory enzyme indoleamine-2, 3-dioxygenase (IDO) have been linked with short survival of myeloma patients, whereas, endogenously produced IDO showed detrimental effect on immune surveillance. In contrast, IDO induction in highly proliferative diseases starves the rapidly growing myeloma clone in MSCs, for the formulators’ positive assets. In future, the modulation of the myeloma bone marrow niche by primed MSCs may further refine this technique for the direct antitumor/anti-myeloma therapeutics (Peiffer et al., 2012). Currently, Completion Lymph Node Dissection (CLND) is a standard of care in patients with a positive sentinel node, although it has various side effects such as infection, wound complications and lymphedema. The data collected from a review of the National Cancer Data Base, revealed that 50% patients were undergoing a completion dissection with a positive SLN in 2004-2005 (Hardin and Lange, 2012). Ipilimumab (human IgG1 Mab-monoclonal antibody), hydroxyurea, dacarbazine, high-dose IL-2 and vemurafenib drugs were approved by FDA for metastatic melanoma. When patient’s melanomas express the BRAF V600E or C-Kit (receptor tyrosine kinase) mutations, targeted therapies vemurafenib or imatinib can be offered. In melanoma patients vemurafenib, was found significantly efficient by showing 50-70% response rate in advanced disease by targeting serine-threonine kinase, whereas, ipilimumab immunotherapy displayed enhanced survival and durable tumor regressions (Flaherty et al., 2010; Robert et al., 2011; Curti and Urba, 2012).

**Non-melanoma skin cancers:** Non-melanoma skin cancers (NMSCs), Squamous Cell Carcinomas (SCCs) and Basal Cell Carcinomas (BCCs) account for 95% of all skin cancers in solid Organ Transplant Recipients (OTRs) due to increased immunosuppressive load and decreased immune surveillance. Frequency of NMSCs after OTRs is mainly depending on the duration and intensity of immunosuppressive treatments (Christenson et al., 2011). Regular use of broad-spectrum sunscreens (minimum SPF of 30 and higher), sun protective clothing, wide-brimmed hats, sunglasses and other additional measures can reduce UV exposure and helps in preventing AKs actinic keratoses and SCCs in the skin (Thompson et al., 1993). Utilization of strong sunscreens (SPF>60) is recognised as an effective in preventing the development of new SCCs and AKs in single centre prospective study on 60 OTRs (Ulrich et al., 2009). Topical imiquimod, an immunomodulator exert antiviral and antitumor activities via activation of the toll-like receptor 7 (TLR-7) and found effective in treating AKs in immune-compromised individuals (Ulrich, 2009). Due to increased activity of inflammatory prostaglandins and enzymes during sun damaging of skin, AKs and SCCs, a non-steroidal anti-inflammatory drugs (NSAIDs), like diclofenac (3%) has been shown quite efficient in treating AKs in the non-transplant patients (Lonsdorf et al., 2010). Photodynamic therapy (PDT) associated with aminolevulinic acid (ALA) could be used as an effectual treatment for prevention of additional SCCs in high-risk OTRs (Babilas et al., 2010; Willey et al., 2010).

**Glioblastoma:** Various remedial approaches have been used for the treatment of GBM or Grade IV glioblastoma, such as chemotherapy, radiation, surgical resection, radiosurgery, corticosteroids, antiangiogenic therapy and gene transfer (Tai and Kasahara, 2008; Kolata and Ahman, 2009). Platelet-directed therapies for the treatment of glioblastoma and individualised platelet-level-based dosing guidelines can be worth explored in further studies due to occurrence of a direct correlation between platelet levels and survival rate of patients. During the study, 84 patients showed 17.6 months median overall survival with a significant reduction in platelets counts in beginning of 6 week which was further associated with longer survival (Williams et al., 2012). Glioblastoma Multiforme (GBM), have shown rapidly diffuse infiltrative growth and exhibit higher cellular heterogeneity towards therapeutic resistance (Novakova et al., 2009). Vorinostat (a histone deacetylase inhibitor) and olaparib (at sub-cytotoxic-concentration) can also make a possible strategy for targeted therapy for ependymoma, a malignant brain tumor (Van Vuurden et al., 2011; Wright and Gajjar, 2012).

**Colorectal cancer:** Vascular Endothelial Growth Factor (VEGF) plays an important role in angiogenesis and essential for tumor growth, invasion and metastasis (Folkman, 1990; Rak et al., 1995). Anti-VEGF therapies inhibits VEGF mediated signalling pathway and normalized tumor vasculature to facilitate better release of therapeutic means at the tumor site (Jain, 2001).
Bevacizumab (Mab against VEGF) containing irinotecan or oxaliplatin-based drug combinations have present standard of care in the first-line as well as second-line therapy in case of metastatic colorectal cancer (mCRC) (Odabas et al., 2010). In mCRC patients recommended dose of bevacizumab is (5 mg kg⁻¹ every 14 days or 7.5 mg kg⁻¹ every 21 days) given as an IV infusion until disease progression. Due to increasing risk of bleeding, venous thromboembolism and an adverse affect on wound-healing process the dosing schedule of bevacizumab need to clarify. Bevacizumab dose 5 mg kg⁻¹ on every 2 weeks versus 4 weeks in combination with biweekly FOLFIRI regimen had found significant efficiency and acceptability in mCRC patients (Geraci, 2004; Nalluri et al., 2008; Sher et al., 2009; Yildiz et al., 2012). Systemic anti-angiopoietin-2 therapy in combination with L1–10 (a peptide–Fc fusion protein at the dose of 4 mg kg⁻¹, thrice weekly) can prove a beneficial strategy to overcome the metastatic malignancies and in the setting of minimal residual disease (Tressel et al., 2008; D’Souza et al., 2012). Radioembolization (utilization of percutaneous transarterial techniques for injecting radioisotope loaded micron-sized embolic particles) has found effective in 45 colorectal cancer patients with 408 days of median survival and 81% maintained stable disease without showing any life-threatening or fatal toxicities (Goin et al., 2003; Wong et al., 2005). Colorectal liver metastases (121 patients, best survival first or second line chemotherapy) and hepatic colorectal metastases (463 patients, best survival in treatment 4-week intervals) have shown 2% partial response rate (PR), 3 months time-to-progression (TTP), 9 months median overall survival and 14.7% PR, 62% 1-year survival rates, 28%, 2-year survival rates, respectively, after chemorobolization (Vogl et al., 2009; Albert et al., 2011). Intra-arterially delivered drug-eluting beads found to be safe and efficient in metastatic colorectal cancer (Martin et al., 2011). Regorafenib, an oral tyrosine kinase inhibitor targets various receptors such as VEGFR1-2, PDGFR beta, FGFR and KIT along with other key elements of signal transduction pathways and found to be effective against third line metastatic colorectal cancer and showing longest progression free rate in gastro-intestinal stromal tumors than any other tested drug in a phase III study (George et al., 2011). Nilotinib (an oral tyrosine kinase inhibitor) active in some imatinib resistant forms of KIT, inhibits BCR-ABL, KIT and PDGFRs and confers promising activity in imatinib and sunitinib resistant GIST in a phase I study (Montemurro et al., 2009).

Oesophagus and gastro-esophageal-junction (GEJ): Cancers of the oesophagus and Gastro-esophageal Junction (GEJ) generally occurs in the middle or upper one-third of the oesophagus (squamous cell carcinoma) or in the lower one-third or junction of the oesophagus and stomach (adenocarcinoma) (Tejani and Burtness, 2012). Patients with localized oesophageal cancer treating with preoperative cisplatin, 5-FU and 44 Gy radiation followed by three cycles of postoperative cisplatin and paclitaxel has been shown 40% (5 years) survival and 49% disease-specific survival in non-cross resistant postoperative chemotheraphy in a phase II study (Heath et al., 2000; Kleinfelder et al., 2003). Epidermal Growth Factor (EGFR) and Vascular Endothelial Growth Factor (VEGF) inhibitors, surgically unresectable associated with bevacizumab, cisplatin, irinotecan, docetaxel, cisplatin and 5-FU may found most potential targets and show effectiveness in phase II trial and (Kleespies et al., 2004; Kelsen et al., 2009; Shah et al., 2006; Wang et al., 2007). Combined association of Nanog sRNA, a core marker of CSC (cancer stem cells) and cisplatin enhanced chemosensitivity was found to be positively correlated with TNM stages and histopathological differentiation of ESCC patients (Du et al., 2012). Finest treatment approach needs further research, although induction chemotherapy before preoperative chemoionisation and postoperative adjuvant chemothepapeutic strategies strengthen systemic therapy delivery (Tejani and Burtness, 2012).

Gastric cancer and lung cancer: Although trastuzumab, conjugate trastuzumab emtansine and EGFR/HER2 blockade with lapatinib may yield positive results with overall survival against this molecular heterogeneity malignancy, an intensive research is needed for designing novel targeted agents such as MET/HGF (MET receptor/ hepatocyte growth factor) and FGFR (fibroblast growth factor receptor) for better clinical development and future treatment options for gastric cancer (Wu et al., 2009, Smyth and Cunningham, 2012). Cetuximab (partially humanised murine Mab), shows minimal activity as a single agent targeted therapy, whereas, its combination with doublet chemotherapy and three discrete chemotherapy backbones presented significant increase in response rate (3%) and median overall survival (3.1 months) (Pinto et al., 2009; Chan et al., 2011). In metastatic and sporadic GISTs (gastrointestinal stromal tumors) adjacent imatinib (a KIT tyrosine kinase inhibitor) is recommended as the standard treatment (Chan et al., 2012). Imatinib and sunitinib exerts antitumor activity in some patients which were found for carrying mutations in exons 11 or 13 (Guo et al., 2011; Minor et al., 2012). Sunitinib malate, (tyrosine kinase inhibitor) is used in the treatment of advanced renal cell carcinoma and GISTs. Currently reported, another immunomodulatory drug fingolimod contain some anti-angiogenic properties and potentiate the effects of sunitinib malate (Mousseau et al., 2012). Inhibition of
UbcH10 (a family member of ubiquitin-conjugating enzyme) leads to significant enhancement in the chemosensitivity towards SK-MES-1 (lung cancer cell lines) cells for gemcitabine/paclitaxel drugs and can be used for prediction of clinical efficacy of chemotherapeutic treatments due to susceptibility for drugs (Zhao et al., 2012). Boronate proteasome inhibitor PS-341 significantly block the binding of leukemia and melanoma tumor cells to activated endothelial cells and reduced the number and size of lung metastases in Lewis lung tumor bearing mice (Teicher et al., 1999).

**Leptomeningeal metastases:** Target behind treatment of Leptomeningeal Metastases (LM) from NSCLC is not to cure but to extend survival and maintain good quality of life (Nagpal et al., 2012). Capecitabine, afatinib and dabrafenib found to be quite effective against brain metastases although later two are associated with cutaneous side effects (Paydas et al., 2009; Anforth et al., 2013). A combination of afatinib and cetuximab explore >90% overall response rate (Yap et al., 2010; Janjigian et al., 2011). Intrathecally administrated mafosfamide (a cyclophosphamide-like alkylating agent) has been shown efficacious and tolerable in phase I trial of IT therapy with liquid tumors and primary brain tumors (Blaney et al., 2005). Bevacizumab associated with pemetrexed been has been established as an efficient drug in reducing edema surrounding brain metastases (Levin et al., 2011).

**Hepatic Metastatic Disease (HMD):** For the treatment HMD among four pillars of oncologic treatments including surgical, medical, radiation and interventional oncology, surgical treatment remains the most favourable remedial choice, however, most of the patients don't get this facility timely due to diffuse nature of disease and large tumor burden. Chemoembolization and radioembolization, are transarterial Locoregional Therapies (LRTs), based on catheterization of tumor feeding artery and targeted delivery of toxic agents, have been preferred due to maximum survival, response and quality of life in hepatic metastatic disease (Salem et al., 2010, 2011). Liver transplantation has shown an immense potential for treatment of cirrhotic patients with Hepatocellular Carcinoma (HCC) within the Milan criteria. But due to shortage of donor organs, the disease succession threat left the waitlisted patients beyond transplant criteria. Therefore, sorafenib therapy in combination with locoregional therapy is preferred and it limits the waitlist dropout (Vagefi and Hirose, 2013).

**Osteosarcoma:** Epidemiology of osteosarcoma was reported by Ottaviani and Jaffe (2009). Primary treatment of this malignant bone tumor relies in surgery and chemotherapy but it required more effective and safer management due to higher cytotoxic effects (McAllister et al., 2004). A combination of β-celmene (active component of Chinese traditional herb) and HIF-1 inhibitor (Hypoxia-inducible factor-1, a nuclear transcription factor under hypoxic conditions in normal cells and tumor cells) can become a prevailing option in making therapeutic strategies for effective treatment of osteosarcoma (Barrero et al., 2011; Li et al., 2011; Liang et al., 2012). Denosumab (human antibody) inhibits bone destruction and giant cells via inhibition of RANKL (receptor activator of nuclear factor kappa-B ligand) ligand, also known as tumor necrosis factor ligand superfamily member 11 (TNFSF11); TRANCE a novel ligand of the tumor necrosis factor receptor family has been found to activate c-Jun N-terminal kinase in T cells (Anderson et al., 1997; Wong et al., 1997; Thomas et al., 2010).

**Breast cancer:** Breast cancer patients with positive receptor chemotherapy is normally recommended for vinorelbine, gemcitabine, capecitabine, anthracyclines and taxanes, as a single agent or in combination, however, till now, none of them have proved gold standard, clearly (Verma and Clemens, 2007). Taxanes including paclitaxel and docetaxel (cell mitosis inhibitors) and capetitabine have become the most commonly used chemotherapeutic agents despite of their adverse incident profiling due to profound impact on overall survival (Kamal et al., 2012). Capecitabine (an oral fluoropyrimidine prodrug and farnesyl transferase inhibitor) has found clinically more effective in treating MBC (metastatic breast cancer) patients with a 25% response rate as compared to tipifarnib-capecitabine combination (Li et al., 2012). HER-2 (human epidermal growth factor receptor-2), protein contributes to malignant transformation in breast and other cancers in the presence of HER-2 protein. SGP-1 (antibody against extracellular domain of the HER-3 receptor) can found to be effective in neuregulin stimulated growth of cultured breast cancer cells. HER-2 inhibitors like humanised Mab Herceptin, or SMTKI (small molecule tyrosine kinase inhibitors) and lapatinib are now licensed treatment regimen for breast cancer patients (Blackburn et al., 2012).

A combination of two regimens including trastuzumab, bevacizumab (anti-VEGF-A monoclonal antibody), lapatinib and trastuzumab were found to be effective in reducing xenograft tumor volume as compared to single agent treatment (Epstein et al., 2002; Blackwell et al., 2010). Pestrin et al. (2012) evaluated the lapatinib efficacy and its activity in patients which are already treated with lapatinib (1500 mg day⁻¹), carrying HER-2 negative primary tumors and HER-2 positive circulating tumor cells (CTCs) in MBC. Taxanes
associated with anthracyclines is a keystone for treatment with significant clinical benefit, enhanced metastatic setting, improved survival, 50% overall response rates, 6 months' time to progression rates and 10.4 to 16 months median OS (overall survival) rates in anthracycline-resistant or pre-treated metastatic breast cancer (Toulmonde et al., 2012). Primary chemotherapy containing trastuzumab in combination with paclitaxel (weekly administration) followed by FEC-75 (fluorouracil 500 mg m⁻², epirubicine 75 mg m⁻² and cyclophosphamide 500 mg m⁻²) is found to be quite effective in HER-2 positive breast cancer patients (Pernas et al., 2012). Various new HER-2 targeted agents like lapatinib and pertuzumab associated with trastuzumab or chemotherapy indicates dual HER-2 blockade approach with a completely new area for novel drugs and targeted therapies (Untch et al., 2010; Baselga et al., 2012; Gianni et al., 2012). Alkylphosphocholines and erufosine, a new class of drug has sustained anti-proliferative activity in two breast cancer cell lines (in vitro) and significant cytotoxicity in methylisnotrosurea induced rat mammary carcinoma (in vivo) (Dineva et al., 2012). Erufosine in combination with an anti-BSP antibody was found to decline in the severity in osteolytic lesions persuaded by MDA-MB-231 cells in a human breast cancer skeletal metastasis model in nude rats whereas alkylphosphocholines has shown significant sensitivity against human KB squamous cell carcinoma xenograft (Bauerle et al., 2006). Therefore, erufosine can make a candidate therapeutic agent for treating human malignancies in clinical trials, although a phase II study was started in CLL (chronic lymphocytic leukemia) patients, recently (Yosifov et al., 2007; Konigs et al., 2010).

**Spinal metastasis:** Treatment of spinal metastasis multimodal strategies are used like Radiation Therapy (RT), Bisphosphonates (BPs) and surgery; however alternative minimally invasive local treatments are needed for proper reduction of tumor burden, improvement in vertebral structural integrity, minimizing injury to the neural elements. Lo et al. (2012) evaluated the effectiveness of the combination of PDT (minimally invasive drug-light combination therapy) with RT and revealed that it can ablate vertebral tumors, enhance bone formation, preserve spinal cord, therefore, prove as a viable adjuvant treatment for spinal metastasis after in depth investigation. Various preclinical and clinical studies evaluated the role of DNA-damaging agents (poly-ADP-ribose and platinum salts) in exhibiting increased sensitivity against BRCA-associated (breast cancer type susceptible protein) breast cancers (Kennedy et al., 2004; Michalak and Jonkers, 2011). In total 83% PCR rate (pathologic complete response), was shown by 12 carriers receiving cisplatin, whereas 17% PCR rate was by revealed 76 carriers receiving anthracycline-based treatment (with or without a taxane) in BRCA-1 mutation (Byrsk et al., 2010). Six-thioguanine (6TG) was recognized as a potent antagonist of BRCA2-mutated cells and kill tumors as well as cells that have shown expanded resistance to PARP (Poly-ADP-ribose polymerase) inhibitors or cisplatin through genetic reversal of the BRCA-2 gene. Alkyllating agents cyclophosphamide and CMF therapy (cyclophosphamide, methotrexate, fluorouracil) has shown minor antitumor activity and low effectiveness against BRCA1-mutated human breast cancer xenografts, whereas, BRCA-2 deficient mammary tumors displayed higher sensitivity to chlorambucil, melphalan and ibutumine (Dorawho et al., 2007; Evers et al., 2010; Issacva et al., 2010). Total 6 patients out of 40 associated with metastatic breast cancer stayed on complete reduction after 56+ to 150+ months using high dose chemotherapy in BRCA-1 and BRCA-2 mutations (Vollebergh et al., 2009; Pessetto et al., 2012). Triple-negative breast cancer do not benefit from available targeted therapy due to lack of Estrogen Receptor (ER) and Progesterone Receptor (PR) expression and the absence of HER2/neu gene amplification, therefore a selective new targeted drug is required in modern oncology (Grobb et al., 2012). A-27808 and MCF-7 cell lines effectively potentiate the cytotoxicity of platinum combination with histone deacetylase inhibition treatment with increased levels of DNA damage and decreased BRCA1 mRNA levels (Weberpals et al., 2009). Histone deacetylase inhibition is completely novel therapeutic means towards sensitization for breast cancer cells, especially BRCA-1/2, drug resistant mutated tumors (Kim et al., 2003; Bayraktar and Gluck, 2012).

A combination of vorinostat, aurora kinases inhibitor (MK-0457 or MLN8237) characterized a new remedial approach for the treatment of Aurora A-amplified and/or triple negative breast cancers both in vitro and in vivo (Fiskus et al., 2012). Due to carrying BRCA-1 gene mutation by triple-negative breast cancers, they are highly sensitive towards platinum compounds, whereas platinum associated with cetuximab (chimeric mouse/human Mab) directed against epidermal growth factor (EGFR), increased its response rate from 30 to 49% (Carey et al., 2007). PARP inhibitor and tamoxifen or aromatase inhibitors were found to be effective and increased the overall survival of about 82% of patients after 8 years of treatment, respectively (Telli and Ford, 2010; Girgert et al., 2012). Adjuvant tamoxifen has been proved beneficial by 40% in decreasing breast cancer mortality in women more than 70 years of age, whereas aromatase inhibitors have proven more beneficial than tamoxifen with fewer side effects in post-menopausal breast cancer women (Kanapuru et al., 2012). Selective
Estrogen Receptor Modulators (SERMs) and arzoxifene are found to be effective in reducing the frequency (38% for all breast cancers and 48% for ER-positive cancers) of invasive ER-positive breast cancer in postmenopausal women with low bone mass or osteoporosis (Pawelek et al., 2012). SERMs tamoxifen and raloxifene can also prevent the risk of developing primary invasive breast cancer pre and post menopausal women.

**Prostate cancer:** For the treatment of prostate cancer mostly Androgen Deprivation Therapy (ADT) is used but due to increasing undesirable consequences and some negative effect of this regimen Helical Tomotherapy (HT), a novel 3D conformal radiation therapy based on modulation of IMRT (intensity-modulated radiation therapy) has been recommended. In this technique treatment beams are spatially and temporally modulated to maximize the delivered dose at tumor site, whereas, minimizing the dose delivered at normal tissues or structures with low rates of acute and late toxicities (Kapatoes et al., 2001; Alicikus et al., 2011). Helical tomotherapy associated with androgen deprivation therapy has shown excellent biochemical disease-free survival, whereas, helical tomotherapy concomitant with superior dose distributions and image guided radiation therapy has found to be better option for high-dose external beam radiation therapy and become a good choice for proper treatment of localized prostate cancer (Tomita et al., 2012).

**Diffuse large B cell Lymphoma:** Rituximab (an IgG chimeric Mab) has found to be exhibit antitumor activities via antibody-dependent cellular cytotoxicity, complement-mediated cytotoxicity, stimulation of anti-proliferation and apoptosis and apoptotic cell death through NF-jB signalling pathway (Dcaus et al., 1993; Shan et al., 1998). A combination of CDC7 inhibition with rituximab have shown a significant higher rate of apoptosis in ly3 cells (subtype cells) and found to be a new therapeutic strategy (specifically for rituximab resistant patients) for the treatment of DLBCL (diffuse large B cell lymphoma) (Jaffe et al., 2001; Chu et al., 2006; Hou et al., 2012).

**Soft tissue sarcomas and anaplastic thyroid cancer:** Treatment of Soft Tissue Sarcomas (STS) relies in new therapeutic agents like trabectedin which has shown 50% response rate, 24% partial response rate and 13% pathological complete remission rate in myxoid liposarcoma during neoadjuvant phase II study (Grosso et al., 2009). Eribulin mesylate has been shown 12 weeks Progression-free Rate (PFR) in liposarcoma, leiomyosarcoma, synovial sarcoma and other STS with the rate of 47, 32, 21 and 19%, respectively (Schoffski et al., 2011). Pazopanib (synthetic indazolopyrimidine) drug which targets multiple kinases such as VEGF and PDGF has shown 12 weeks progression-free rate in leiomyosarcoma (44%), synovial sarcoma (39%), liposarcoma (26%) and other types of STS (39%) in stratified phase 2 clinical trial (Slieijfer et al., 2009). Masitinib found to be inhibiting mast cells in systemic mastocytosis in dogs and humans with currently, 97% disease control rate and 41.3 months progression-free survival (PFS) in metastatic GIST in first line phase II study (Le Cesne et al., 2010). Sorafenib has shown a modest level of activity against angiosarcoma, leiomyosarcoma and osteosarcoma in II trials study through a strong inhibition of tyrosine kinase inhibitor like VEGF, PDGF, c-KIT and the RAF seronine/threonine kinase (Chow and Eckhardt, 2007; Silk and Schuetze, 2012). Sunitinib significantly reduce the growth of ATC (anaplastic thyroid cancer) by direct inhibition of its molecular target VEGFR-2 in orthotopic mouse xenografts (Wong et al., 2012). Sunitinib treated patients have shown prolonged disease stabilization in well differentiated thyroid cancer (WDTC), even in the case of distant metastasis (Davson et al., 2008; Cleary et al., 2010; Kaldymides et al., 2010).

**CONCLUSIONS AND FUTURE PROSPECTS**

Developed new therapies have sensitized tumor cells, towards different chemotherapeutic drugs and agents. Tumor progression has also increased due to development of multiple drug resistance by a variety of different mechanisms. Towards this, highest benefits can be achieved by utilizing combinatorial therapies as compared to single one. A combination of erusfon as an alkylphospholocholine based cytostatic drug with cisplatin and 5-fluorouracil displayed additive efficiency regarding enhancement of anti-cancerous property as well as to overcome the resistance against various therapeutics in patients with progressive disease (Kapoor et al., 2012). Over dose can cause adverse effects on patient's health taking anti-angiogenic agents. Therefore, it becomes necessary to optimize the dose of variable chemotherapeutics according to tumor type, location, growth rate, previous therapy, genotype of the patients, historical background, drug interactions, pharmacology and other variables for getting maximum benefits with highest tolerable dose and optimum biological activity regarding elimination of cancer cells. Drugs with slow clearance and long bioavailability can hamper the affectivity of other regimens in a long term schedule. Synthetic drugs currently used in the clinical management create obstructions with fundamental biological mechanisms and causes devastating side effects. In order to overcome this problem strict regimen exercise has been proposed and examined as a praising therapeutic modality for getting physical, physiological and psychosocial settlement. In future, detailed
explorations with other standard chemotherapy regimens are required for proper clinical utilization in overcoming this deadly disease progression for a safe cure.

ACKNOWLEDGMENTS

Ms. Alpaka Kulhari thanks Council of Scientific and Industrial Research (CSIR, New Delhi) for Senior Research Fellowship. Mr. Arun Shrirayan thanks Haryana State Council for Science and Technology (HSCST, Panchkula) for Junior Research Fellowship. The Bioinformatics Infrastructure Facility developed under BIF Program, Transgenic Greenhouse and Tissue culture facility established under FIST program, sanctioned to Prof. A. Chaudhry by the Department of Biotechnology (DBT) and Department of Science and Technology (DST), Ministry of Science and Technology, Government of India, New Delhi is duly acknowledged.

REFERENCES


Untch, M., S. Loibl, J. Bischoff, H. Eidtmann and M. Kaufmann et al., 2010. Abstract S3-1: Lapatinib vs trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy: Primary efficacy endpoint analysis of the GEPARQUINTO STUDY (GBG 44). Cancer Res., Vol. 70. 10.1158/0008-5472.SABCS10-S3-1


