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

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ABSTRACT

Background: Cancer is now becoming most prevalent human disease requiring early detection, prevention, diagnosis and effectual cure. Defect in apoptotic signaling and up-regulation of drug transporters in cancer cells significantly limit the effectiveness of cancer chemotherapy. Complex signaling network involving multiple proteins 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

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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 200 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

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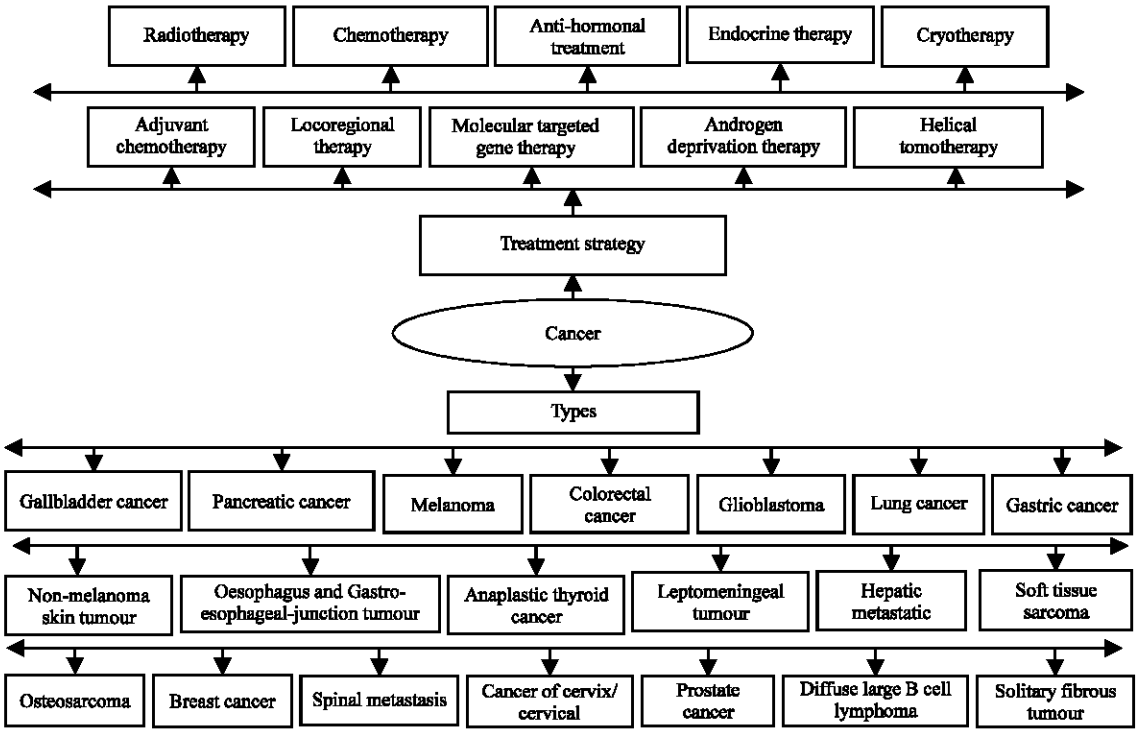

Fig. 1: Schematic overview depicting twenty different types of cancer and their treatment strategies

against different drugs (Bayraktar and Gluck, 2012). Currently various therapeutic strategies for treating cancer via blockage 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-κB, 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 (Aggarwal *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 Glivec (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 Glivec 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; Zatonski *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 1: List of curing managements against different types of cancer through targeted chemotherapies

Type of cancer					
Melanoma	Completion lymph node dissection	Surgery	Infection, wound complications and lymphedema	Current standard of care for patients with a positive sentinel lymph node	Hardin and Lange (2012)
Metastatic melanoma	Ipilimumab (human IgG1 Mab) and vemurafenib and ipilimumab immunotherapy	Vemurafenib used as targeted therapies against serine-threonine kinase and Ipilimumab used as immunotherapy	Main toxicities associated with vemurafenib are arthralgias, rash, fatigue, peripheral facial palsy and a difficult to overemphasize photosensitivity	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	Curti and Urba (2012)
Metastatic melanoma	Three drugs (hydroxyurea, dacarbazine, and high-dose IL-2	Synthetic drug and cytokinines	High- dose IL-2 caused hypotension and severe organ dysfunction	Overall survival have never determines and very small number of patients are treated due to unavailability of expertise management regarding IL-2-related toxicities	Curti and Urba (2012)
Brain metastases	Combination of SRS and whole brain radiation therapy (WBRT)	Utilized multiple cobalt sources and radiation	Associated with ong-term toxicities in WBRT with long-term survivals	Conferred more survival benefit as compared to surgery or radiation alone in selected patients	Curti and Urba (2012)
Grade IV glioblastoma	Radiotherapy plus concomitant and adjuvant temozolomide (RCAT)	Imidazotetrazine derivative of the alkylating agent dacarbazine	Nausea, vomiting, thrombocytopenia and leukopenia	Found to be effective regarding long term survival in the phase III trial with decreased platelet count, 12.1 months progression free survival and 14.6 months overall survival.	Williams *et al.* (2012)
Metastatic colorectal cancer; Secondary CNS malignancies	Bevacizumab	Bevacizumab (humanized Mab)	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)	It is recommended (5 mg kg^{-1} every 14 days or 7.5 mg kg^{-1} every 21 days) that the drug should not be started for at least 4 weeks after a major surgery or until the surgical incision is completely healed; increasing risk of venous thromboembolism in cancer patients receiving bevacizumab	Geraci (2004), Nalluri *et al.* (2008) and Sher *et al.* (2009)
Cancers of the esophagus and gastroesophageal junction	Surgically unresectable associated with bevacizumab (against VEGF), cisplatin, irinotecan, docetaxel and 5-FU	Surgery combined with synthetic drug	Higher dose of Bevacizumab can cause adverse events viz., bleeding, hypertension, thromboembolism, fistulization and perforation were rare	Quite effective in phase II trial in adenocarcinoma of the esophagus	Kelsen *et al.* (2009), Shah *et al.* (2006) and Yildiz *et al.* (2012)
Metastatic colorectal cancer	Bevacizumab in combination with biweekly FOLFIRI regimen	Bevacizumab (humanized Mab) and FOLFIRI regimen is a chemotherapy treatment (folinic acid, 5-FU, irinotecan)	Bleeding, hypertension, thromboembolism, fistulisation and perforation	Quite effective with high efficacy and tolerable	Yildiz *et al.* (2012)
Colorectal cancer	Radioembolization	Utilization of percutaneous transarterial techniques for injecting radioisotope loaded micron-sized embolic particles	No life-threatening or fatal toxicities	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	Goin *et al.* (2003) and Wong *et al.* (2005)
Metastatic colorectal cancer	Regorafenib (an oral tyrosine kinase inhibitor)	Targets multiple receptors viz., VEGFR1-2, PDGFR beta, FGFR1 and KIT	Hand-foot skin reactions and hypertension	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)
GIST	Nilotinib	An oral tyrosine kinase inhibitor which inhibits BCR-ABL, KIT and PDGFRs	Fatigue and gastrointestinal complaints	Following drug contain promising activity in imatinib and sunitinib resistant GIST in a phase I study	Montemurro *et al.* (2009)

Table 1: Continue

Type of cancer					
Esophageal cancer	FOLFOX chemotherapy with bevacizumab	Bevacizumab (humanized monoclonal antibody against VEGF)	Common side effects associated with bevacizumab are: Bleeding, hypertension, thromboembolism, fistulisation and perforation	Found 2 year disease-free survival after treatment (eight weeks following resection with a further six cycles of FOLFOX/bevacizumab)	Tejani and Burtness (2012)
Gastric cancer	Cetuximab combined with doublet chemotherapy and three discrete chemotherapy	Cetuximab (partially humanised murine Mab and radiation sensitizer)	Cetuximab are acne like rashes photosensitivity, hypomagnesemia and less commonly pulmonary and cardiac toxicity	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 (3%, 3.1 months), (41-63%, 9-16.6 m) and more than 50%, respectively.	Pinto *et al.* (2009) and Chan *et al.* (2011)
Metastatic gastrointestinal stromal tumours	Targeted therapy with imatinib	Imatinib (inhibitor of receptor tyrosine kinase enzyme)	Common side effects are weight gain, reduced number of blood cells (neutropenia, thrombocytopenia, anemia), headache, edema, nausea, rash and musculoskeletal pain	Standard treatment	Chan *et al.* (2012)
Sporadic1 gastrointestinal stromal tumours	Adjuvant therapy with imatinib	Imatinib (inhibitor of receptor tyrosine kinase enzyme)	Common side effects are weight gain, reduced number of blood cells (neutropenia, thrombocytopenia, anemia), headache, edema, nausea, rash and musculoskeletal pain	Effective treatment but mixed results are obtained when associated with NF-1	Chan *et al.* (2012)
Advanced renal cell carcinoma and gastrointestinal stromal tumors	Sunitinib malate with immunomodulatory drug fingolimod	Sunitinib malate is a multitaregetd receptor tyrosine kinase inhibitor and fingolimod is a sphingosine-1-phosphate analog	Generally some side effects are associated with sunitinib therapy are fatigue, diarrhea, nausea, anorexia, hypertension, a yellow skin discoloration, hand-foot skin reaction, and stomatitis, although. This dual therapy did not exhibit any cumulative toxicity	This combined orally administered drugs decreased rat breast tumor growth with providing an effective means of reducing tumor angiogenesis	Mousseau *et al.* (2012)
Leptomeningeal metastases	Capecitabine	Capecitabine (an oral prodrug and an antimetabolite of cell division inhibitor)	General side effects of Cetuximab are acne like rashes photosensitivity, hypomagnesemia and less commonly pulmonary and cardiac toxicity	Following strategy revealed the efficacy of drug in LM and brain metastases from breast cancer and LM in NSCLC	Paydas *et al.* (2009)
	Afatinib	Irreversible EGFR inhibitor	Afatinib can causes rash, diarrhoea and elevations in transaminases	Found effective in brain metastases from NSCLC, whereas combination strategy in gefitinib or erlotinib resistant tumors had a shown >90 % overall response rate systemically	Yap *et al.* (2010) and Janjigian *et al.* (2011)
	Combination of Afatinib and Cetuximab	Cetuximab (partially humanised murine Mab and radiation sensitizer)			

Table 1: Continue

Type of cancer					
Liquid tumors and primary brain tumors	Mafosfamide	Cyclophosphamide-like alkylating agent	Drug is under investigation as a chemotherapeutic and several phase I trials have been completed	Intrathecally administrated mafosfamide has been shown efficacious and tolerable in phase I trial of IT therapy	Blaney *et al.* (2005)
Gallbladder cancer	Sorafenib therapy in combination with locoregional therapy	Sorafenib, (a bi-aryl urea) inhibitor of tyrosine protein kinases (VEGFR and PDGFR)	Skin rash, hand-foot skin reactions, diarrhoea and hypertension	Found to be effective in to preventing waitlistd dropout for further liver transplantation	Vagefi and Hirose (2013)
Osteosarcoma	Combination of HIF-1 inhibitor and β-elemene	β-elemene, from Chinese traditional herb	Innovative drug, with fewer side effects	β-elemene and inhibitors of HIF-1α repressed the viability of human osteosarcoma cells via., induction of apoptosis. Also shown excellent advantages against broad antitumor spectrum viz., lung cancer, prostate cancer and carcinoma	Li *et al.* (2011) and Liang *et al.* (2012)
HER-2 positive breast cancer	Primary chemotherapy containing trastuzumab in combination with paclitaxel and FEC-75	Trastuzumab (Mab directed against HER-2/neu receptor), paclitaxe (mitotic- inhibitor, discovered from endophytic fungi in the bark)	Hematologic toxicity, neutropenia, febrile neutropenia, ischemic stroke, pulmonary embolism, atrial fibrillation. Although, some were successfully treated	Found to be effective at a median follow-up of 50.2 months in a non-clinical trial setting	Verma and Clemons (2007) and Telli and Ford (2010)
Metastatic breast cancer	Lapatinib and pertuzumab associated with trastuzumab	Trastuzumab (Mab directed against HER-2/neu receptor), Lapatinib (tyrosine kinase inhibitors) and pertuzumab (Mab)	Showed no increase in cardiac toxic effects	These HER-2 targeted agents indicate dual HER2 blockade approach with a completely new area for novel drugs and targeted therapies	Untch *et al.* (2010), Dineva *et al.* (2012) and Gianni *et al.* (2012)
BRCA1-Deficient breast cancer	Poly (ADP-ribose polymerase and platinum salts	Both are DNA-damaging agents	Generally platinum based monotherapy are with toxicity and poor oral bioavailability	Further research is needed for preclinical testing of (combinations of) therapeutic agents for improvement in treatment strategies because these tumours can exert resistance to these drugs	Kennedy *et al.* (2004) and Byrski *et al.* (2010)
Triple-negative breast cancers	Platinum associated with Cetuximab	Cetuximab (chimeric mouse/human Mab)	General side effects of Cetuximab are acne like rashes photosensitivity, hypomagnesemia and less commonly pulmonary and cardiac toxicity	Found to be sensitive towards platinum compounds,whereas combination increased its response rate	Carey *et al.* (2007)
	Tamoxifen or aromatase inhibitors	Tamoxifen (anti-estrogenic)	Main side effects are bone loss, thromboembolism, reduced cognition	Following treatment was found to be effective and increased the overall survival and proved an appropriate targeted therapy. However more research is needed with higher affinity and good bioavailability before any clinical trials	Telli and Ford (2010) and Girgert *et al.* (2012)
Breast cancer	Adjuvant tamoxifen	Tamoxifen (anti-estrogenic)	Some treatment toxicity (osteoporosis and joint disorders such as arthritis, arthrosis and arthralgia.) was exerted on survival with both the treatments	Aromatase inhibitors have proven more beneficial than tamoxifen fewer side effects in post menopausal breast cancer women.	Kanapuru *et al.* (2012)

Table 1: Continue

Type of cancer					
ER-positive breast	Arzoxifene	Arzoxifene (selective estrogen receptor modulators (SERMs)	Some side effects viz: venous thromboembolism, vasomotor symptoms, muscle cramps, and some gynecological events was found with arzoxifene treatment	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 osteoporosis, although detailed clinical research is required for development of the drug in future	Powles *et al.* (2012)
Advanced renal cell cancer	Pazopanib (synthetic indazolpyrimidine)	Targets multiple kinases, viz., VEGFR1-3 and PDGFR	Fatigue, diarrhea, nausea, weight loss and hypertension	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	Hou *et al.* (2012)
Metastatic GIST	Masitinib	An oral tyrosine kinase inhibitor	Rash, asthenia, diarrhoea, nausea and muscle cramps	Showed 97% disease control rate and 41.3 months progression-free survival (PFS) in first line phase II study	Le Cesne *et al.* (2010)
Breast, lung, head, neck and ovary cancer	Cisplatinum, carboplatinum and oxaliplatin	Platinum-based chemotherapeutics	Renal toxicity, hypertension, anemia, reduced fertility and acute leukemia	Intralymphatic delivery induces higher drug concentrations in the retroperitoneal lymph nodes when compared with intravenous administration	Zor *et al.* (2012)

Houry *et al*., 1989). For pancreatic cancer currently most effective anticancer drug gemcitabine is using 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 (Pfeifer *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 Altman, 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 43 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 chemoembolization (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, FGFR1 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 esophagus 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 chemotherapy in a phase II study (Heath *et al*., 2000; Kleinberg *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 siRNA, 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 chemoradiation and postoperative adjuvant chemotherapeutic strategies strengthen systemic therapy delivery (Tejani and Burtness, 2012).

Gastric cancer and lung cancer: Although trastuzumab, conjugate trastuzumab emtansine and EGFR/HER2 blockage with lapatinib may yield positivee 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) adjument 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 chemotherapatic treatmants 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 in patients with liquid tumors and primary brain tumors (Blaney *et al*., 2005). Bevacizumab associated with pemetrexed has 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-elemene (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 patient 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 Clemons, 2007). Taxanes including paclitaxel and docetaxel (cell mitosis inhibitors) and capecitabine 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-3 (human epidermal growth factor receptor-3), 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 methylnitrosourea 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 susceptibility 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 (Byrski *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 reversion of the BRCA-2 gene. Alkylating 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 lomustine (Donawho *et al*., 2007; Evers *et al*., 2010; Issaeva *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 (Grob *et al*., 2012). A-2780s 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 osteoporosism (Powles *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 (Deans *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 indazolpyrimidine) 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 (Sleijfer *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 (Dawson *et al*., 2008; Cleary *et al*., 2010; Kaldrymides *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 erufosine an alkylphosphocholine 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.

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