Old Disease, New Targets
Part-I, Solid malignancies
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Abstract
Targeted agents are now an integral part of treatment regimens for some cancers. Trastuzumab is established in treatment of human epidermal receptor 2 (Her2) positive breast cancers, with improvements in both, the disease free and over all survival. Monoclonal antibody (MoAB) against vascular growth factor receptor (VEGF), bevacizumab and cetuximab a MoAB against epidermal growth factor receptor (EGFR) are establishing their role in a many cancers after making their mark in colorectal cancer. Sorafenib and sunitinib have success stories in renal carcinoma. The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial has established sorafenib role in advanced hepatocellular carcinoma, while in gastrointestinal tumors; imatinib and sunitinib have proven role. At this point in time side effect profile of all these agents appears relatively safe however cost for developing countries remains an issue.

Introduction
After impressive results of rituximab in the treatment of Non-Hodgkins lymphoma, role of Targeted agents in the solid tumors continues to evolve and so does the list of agents available. The current list of available agents includes trastuzumab, bevacizumab, cetuximab, panitumumab, lapatinib, gefitinib, erlotinib, imatinib, sunitinib, and sorafenib (Table). The efficacy of many agents continues to result in improved survival and of many more continues to be investigated.

Trastuzumab:
Approximately 20-30% of invasive breast cancers over-express Her2. Her2 also called erb B-2 receptors belong to a family of EGFR. Generally considered to be a negative prognostic indicator for breast cancer; studies are now focused on assessment of its association with efficacy of other chemotherapeutic agents including alkylating agents. Trastuzumab a MoAB against Her2/neu exerts its action through activating the immune system, increasing the endolysis of Her2, stops receptor dimerization and shedding of extracellular domain. Associated toxicities are infusion related hypersensitivity and cardiomyopathy.1

Trastuzumab for Breast Cancer in adjuvant setting:
HERA (Herceptin Adjuvant), an international trial, accrued >5000 women with Her2 amplified, early stage breast cancer. Patients were randomized to observation (n=1693), trastuzumab for 1 year (n=1694) or 2 years (n=1694) after receiving at least 4 cycles of chemotherapy. More events were observed in observation arm than in treatment arm (220 vs.127, unadjusted hazard ratio (HR), 0.54; p<0.0001) with a benefit of 8.4% at 2 years for disease free survival (DFS) (Figure 1). No survival advantage was observed.2 With a median follow-up of 23.5 months of HERA, more events of recurrence were observed in observation arm (321 vs. 218, p<0.0001). More patients have died in observation arm (90 vs. 53, unadjusted HR, 0.66; p=0.01). Absolute benefit for DFS and over all survival (OS) was 6.3% and 2.7% respectively at 3 years. More women on trastuzumab developed severe congestive cardiac failure (CCF) (p<0.0001) and grade 3/4 adverse events (AEs, p<0.0001).3 No added advantage of continuing therapy for more than one year was observed.

National Surgical Adjuvant Breast and Bowel Project trial B-31( NSABP-B 31) and the North Central Cancer Treatment Group trial N9831 (NCCTG N9831) were the two other trials which demonstrated results in favour of herceptin. The B-31 study compared standard doxorubicin and cyclophosphamide (AC) followed by paclitaxel with same chemotherapy with trastuzumab for 1 year and N9831 compared four cycles of AC followed by paclitaxel for 12 weeks (group 1), 4 cycles of AC and paclitaxel followed by 1 year of trastuzumab (group 2) and 4 cycles of AC followed by paclitaxel and trastuzumab starting together for 1 year (group 3). Combined results of both trials were released. In B-31, 1736 patients and 1615 patients in N9831 were assessable. With median follow-up of 2 years more events were recorded in control group (261 vs. 133, p<0.0001). Absolute differences of 11.8% at 3 years and 18.2% at 4 years for DFS and 2.5% at 3 years and 4.8% at 4 years for OS were observed.4

In Finland Herceptin (FinHer) study, herceptin was used for a shorter period of time with relatively same benefit obtained, although the number of patients accrued was less than the famous HERA trial. Women with Her2 amplified breast cancer were randomized to docetaxel for 3 cycles followed by 3 cycles of 5-Flourouracil, epirubicin and
cyclophosphamide (FEC) with (n = 54) or without trastuzumab (n = 58) or 3 cycles of vinorelbine followed by 3 cycles of FEC with (n = 62) or without trastuzumab (n = 58). Trastuzumab was administered on day 1 of docetaxel or vinorelbine in weekly doses for 9 weeks. Recurrences were less common in trastuzumab group (12 vs. 27, p = 0.01). OS was also better for trastuzumab arm (6 vs. 14 deaths, p = 0.07). Asymptomatic 15% decline in ejection fraction was recorded in 3.5% patients on trastuzumab.

In the Breast Cancer International Research Group 006 trial (BCIRG 006), women with Her2 positive breast cancer were randomly assigned to receive AC followed by docetaxel alone (n=1073), AC followed by docetaxel and trastuzumab for 1 year (n=1074) and docetaxel, carboplatin and trastuzumab for 1 year (n=1075). Second interim analysis revealed better DFS and OS for trastuzumab containing arms with decreased risk of death as well.1,6

<table>
<thead>
<tr>
<th>Drug Name</th>
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<th>Side Effect Profile</th>
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<td>November 2006</td>
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<td>Bevacizumab</td>
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<td>2006</td>
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<td>2008</td>
<td>Metastatic HER2-Negative Breast Cancer</td>
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<td>Cetuximab</td>
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<td>2007</td>
<td>HCC</td>
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**Trastuzumab for Metastatic Breast Cancer:**

In a phase III trial published in 2001 which involved 469 breast cancer patients with metastasis received chemotherapy either AC or paclitaxil both with or without trastuzumab. At the median follow up of 30 months, odds were in favour of trastuzumab in addition to chemotherapy, in terms of time to progression (TTP, 7.4 vs. 4.6 months) and over all response rate (ORR, 50 % vs. 32 % p= <0.001).7

Robert et al8 reported a trial of trastuzumab combined or not to paclitaxil and carboplatin in Her2/neu over expressive metastatic breast cancer patients. ORR was in favour of hereceptin (52% vs. 36%; p = 0.04), improvement in median progression free survival (PFS, 10.7 vs. 7.1 months) and also in OS (38 vs. 31 months) were reported.

**Bevacizumab:**

Vascular granter factor receptor (VEGF) is a
Diffusible glycoprotein produced both by normal and neoplastic cells. It is one of the important regulators for physiologic and pathological angiogenesis. Preclinical studies have demonstrated the efficacy of murine antihuman MoAB against VEGF in suppression of human tumour xenografts. Humanized variant of that murine antibody bevacizumab has been evaluated for various malignancies. Bevacizumab is believed to have a strong angiogenic role. An added advantage of bevacizumab is to decrease elevated interstitial pressure and alter tumour vasculature, by virtue of which it increases the chemotherapy delivery towards tumours.9

**Bevacizumab for Renal Cell Cancer (RCC):**

In a double-blind, phase III trial, patients with metastatic RCC were randomized to bevacizumab and interferon alfa (IFN, n = 327) or IFN and placebo (n = 322). The primary endpoint of OS has not matured till the release of the results while the PFS (10.2 vs. 5.4 months, p = 0.0001), time to treatment failure (TTF, 7.7 vs. 4.4 months, p = 0.0003) and ORR (70% vs. 39%, p = 0.0001) were better for bevacizumab group. Significant AEs in bevacizumab arm were grade 3/4 gastrointestinal perforations, thromboembolic events, hypertension and proteinuria requiring treatment discontinuation.10

**Bevacizumab for Metastatic Colorectal Cancer (mCRC):**

Bevacizumab was granted FDA approval in mCRC on the basis of a phase III trial in which patients with mCRC were treated with irinotecan, 5-Flourouracil (5FU) and leucovorin with or without bevacizumab, with about 50% having had already received a previous therapy. Addition of Becacizumab (AvastinTM) fared better than those without. OS was in favour of bevacizumab arm (20.3 vs. 15.6 months, p<0.001) and reduced the risk of death to 34%. One year OS (74.3% vs. 63.4%, p<0.001), median PFS (10.6 vs. 6.2 months, p<0.001), response rate (44.8% vs. 34.8%, p = 0.004); and the median duration of response (10.4 vs. 7.1 months, p = 0.001) was also better with bevacizumab.9

In Eastern Co-operative Oncology Group (ECOG) study, E3200, patients with mCRC received 5FU, leucovorin and oxaliplatin (FOLFOX) with or without bevacizumab. Confirmed responses were better for combination therapy (22.7% vs. 8.6%, p = 0.0001). Grades 3/4 hypertension, proteinuria, bleeding, vomiting and neuropathy were more common in combination therapy arm.11

**Bevacizumab for Metastatic Breast cancer (MBC):**
Women with MBC were randomized to bevacizumab and capecitabine ($n=232$) or capecitabine alone ($n=230$) in a phase III trial. ORR were better for patients treated with combination therapy ($19.8\%$ vs. $9.1\%$, $p=0.001$), however this did not translate into better PFS or OS.$^{12}$

A phase III study, randomized patients with MBC to receive paclitaxel at $90\,mg/m^2$ on day 1, 8 and 15 q 28 days with bevacizumab at $10\,mg/kg$ on day 1 and 15 ($n=347$) or paclitaxel alone ($n=326$). Combination treatment substantially improved PFS (median, 11.8 vs. 5.9 months, $p<0.001$) and ORR ($36.9\%$ vs. $21.2\%$, $P<0.001$), with no significant improvement in OS (Figure 2). Hypertension, proteinuria, headache, cerebrovascular ischaemia were more commonly seen in bevacizumab arm.$^{13}$

**Bevacizumab for Non-Small Cell Lung Cancer (NSCLC):**

Patients with stage IIIB/IV, NSCLC were enrolled on a phase III trial to receive paclitaxel and carboplatin alone ($n=433$) or with bevacizumab ($n=417$). With a median follow-up of 19 months, median OS is longer for bevacizumab arm ($12.3 \text{ vs. } 10.3 \text{ months, } p = 0.003$), with better 1 and 2 year survival rates $51\%$ vs. $44\%$ and $23\%$ vs. $15\%$ respectively. Substantially improved median PFS (6.2 months vs. 4.5 months, $p<0.001$) and response rate ($35\%$ vs. $15\%$, $p<0.001$) were observed for bevacizumab arm.$^{14}$

**Bevacizumab for Glioblastoma Multiforme (GBM):**

Patients with relapsed GBM received bevacizumab and irinotecan in a phase II study. Of 35 registered patients 23 initial patients received therapy in a 2 weekly fashion and later 12 patients received 6 weekly regimen. Bevacizumab was administered at $10\,mg/kg$ q 14 days for cohort 1 and at $15\,mg/kg$ q 21 days for cohort 2. PR observed by 20 patients and positron emission tomography (PET) scan showed no residual high grade tumour in 6 patients after 1 year of treatment. The 6-months PFS and OS were $46\%$ and $77\%$ respectively.$^{15}$

**Cetuximab:**

EGFR is amplified on many cancers including lung, breast, kidney, colon, prostate, brain, ovarian, pancreatic and head and neck cancers and portrays poor outcome. EGFR is an important mediator for cell proliferation, differentiation, migration, angiogenesis and apoptosis.$^{16,17}$

Cetuximab is a chimeric MoAB with high affinity and specificity for EGFR. It not only halts the receptor mediated effects but also has synergistic effect for chemo and radiotherapy.$^{16,17}$

**Cetuximab for Metastatic Colorectal Cancer (mCRC):**

A European study randomized patients with mCRC to receive cetuximab alone ($n=111$) or with irinotecan ($n=228$). Cetuximab was administered as loading dose of $400\,mg/m^2$ followed by $250\,mg/m^2$ weekly infusion. Intention to treat (ITT) analysis revealed better ORR for combination therapy ($22.9\%$ vs. $10.8\%$, $p = 0.007$). Better disease control was observed with combination therapy ($55.5\%$ vs. $32.4\%$, $p<0.001$). Combination therapy reduced the risk of progression by $46\%$ ($p<0.001$), improved median TTP (4.1 vs. 1.5 months) and median OS (8.6 vs. 6.9 months). Grade 3/4 AEs were more common in combination arm ($p<0.001$).$^{17}$

Another randomized study assigned patients with mCRC to receive best supportive care (BSC, $n=285$) or cetuximab and BSC alone ($n=287$). Patients in treatment arm lived longer (6.1 vs. 4.6 months, HR 0.77, $p = 0.005$). Cetuximab therapy improved PR ($8\%$ vs. $0\%$, $p<0.001$) and SD ($31.4\%$ vs. $10.9\%$, $p<0.001$). AEs were significantly high for treatment group ($p<0.001$).$^{18}$

**Cetuximab for Head and Neck Cancer (HNC):**

An international, phase III study enrolled patients with locally advanced HNC (stage III /IV) to receive radical radiotherapy alone ($n=213$) or with cetuximab ($n=211$). Cetuximab was given as bolus dose of $400\,mg/m^2$ a week earlier of radiotherapy followed by $250\,mg/m^2$ weekly concurrent with radiotherapy for 7 weeks. Combination therapy significantly prolonged the median duration of loco regional disease control (24.4 vs. 14.9 months, HR, 0.68; $p = 0.005$) with control rates of $63\%$, $50\%$ and $47\%$ at 1, 2 and 3 years respectively, versus $55\%$, $41\%$ and $34\%$ ($p<0.01$ at 3 years) (Figure 3A). A $32\%$ risk reduction for loco regional progression was achieved with combination treatment. Median OS improved with addition of cetuximab ($49\%$ vs. $29.3\%$ months) at median follow-up of 4.5 years ($p = 0.03$), with $26\%$ risk reduction for death (HR, 0.74) (Figure 3B).$^{19}$

In all studies described above, patients who received cetuximab; responses were higher for those who developed cetuximab associated skin rash.
Panitumumab:
Panitumumab is fully humanized monoclonal antibody for EGFR which inhibits the EGFR mediated cellular actions like dimerization of the receptor, tyrosine autophosphorylation, tumour growth and induction of apoptosis.\textsuperscript{20,21}

Panitumumab for Metastatic Colorectal Cancer (mCRC):
Patients with chemotherapy refractory mCRC were registered in a phase III trial to receive panitumumab with BSC (n = 231) or BSC alone (n = 232). Panitumumab was administered at 6mg/kg over 60 minutes every other week. From BSC group 176 patients crossed over to treatment arm. Patients in treatment cohort had prolonged PFS (8 weeks vs. 7.3 weeks, p<0.0001) with 46% decrease in relative progression rate (HR, 0.54). After a minimum follow-up of 12 months, more patients in treatment arm achieved PR (10% vs. 0%) and SD (27% vs. 10%). Median response duration was 17 weeks. No significant difference for OS was demonstrated. Approximately 90% patients developed skin related toxicities on panitumumab and grade 3/4 hypomagnesemia in 3% patients.\textsuperscript{21}

Lapatinib:
Lapatinib is an oral tyrosine kinase inhibitor (TKI) with activity against Her2 and EGFR with the added advantage of crossing blood brain barrier. It has shown promising results in breast cancer treatment.\textsuperscript{22}

Lapatinib for Metastatic Breast Cancer (MBC):
In a randomized, phase III trial patients with locally advanced or MBC with Her2 amplification and prior treatment with anthracycline, taxanes and trastuzumab were randomized to receive lapatinib and capecitabine (n = 163) or capecitabine alone (n = 161). More patients had PD in monotherapy arm (HR, 0.49; p<0.001). The median TTP (8.4 vs. 4.4 months) and ORR (22% vs. 14%, p = 0.09) were better for combination therapy. Hand-foot syndrome, diarrhoea, rash, fatigue, nausea and vomiting were common AEs.\textsuperscript{23}

Several trials are ongoing to assess the role of lapatinib in the treatment of breast cancer in adjuvant, neo-adjuvant and metastatic setting.\textsuperscript{22}

Gefitinib:
Targeted therapy against EGFR in NSCLC has shown promising results as second or third line therapy. Gefitinib is an oral selective TKI.\textsuperscript{24}

Gefitinib for Non-Small Cell Lung Cancer (NSCLC):
Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL 1), a phase II, international trial, randomized previously treated NSCLC patients to receive gefitinib at a dose of 250 mg/day (n = 104) and 500 mg/day (n = 106). RR (18.4% and 19%), PFS (2.7 months and 2.8 months) and OS (7.6 months and 8 months) were observed for low and high dose gefitinib respectively. Common AEs were skin rash and diarrhea.\textsuperscript{24}

In IDEAL 2 trial patients with symptomatic NSCLC with stage III/IV or PD were given gefitinib at 250 mg/d (n = 106) or 500 mg/d (n = 115). More than 50% patients...
experienced some relief of their symptoms after 1 week of therapy. Rate of symptom improvement was 43% and 35% for low and high dose respectively. The radiographic responses were 12% and 9% with estimated 1 year survival of 27% and 24% for low and high dose gefitinib respectively. Major toxicities were skin rash and diarrhea. Best responses were achieved for female sex, adenocarcinoma type and non-smokers.

Southwest Oncology Group Study S0126, enrolled patients with stage IIIB/IV advanced bronchioloalveolar carcinoma to receive gefitinib at 500 mg/d. Of 145 accrued patients 101 were chemo-naïve while 45 had received some treatment. After a median follow-up of 22 months PFS was 4 months for chemo-naïve patients and 3 months for previously treated patients. OS at 1 year was 51% for all patients and at 2 year OS was 39% for chemo-naïve patients and 27% for treated patients. Female gender, skin rash, no history of smoking and PS of 0/1 were associated with better responses.

**Erlotinib:**

Erlotinib is an oral TKI and targets EGFR.

**Erlotinib for Non-Small Cell Lung Cancer (NSCLC):**

National Cancer Institute of Canada Clinical Trials Group study (BR.21) accrued patients with progressive NSCLC with previous chemotherapy and randomized them to receive erlotinib (n = 488) or placebo (n = 243). Primary end point was OS. ORR was 8.9% for erlotinib vs. <1% for placebo arm (p<0.001). Patients treated with erlotinib lived longer (median 6.7 vs. 4.7 months, p<0.001). Female gender, Asian race, history of no smoking, adenocarcinoma and EGFR expression were associated with better responses. Skin rash and diarrhoea were most common AEs requiring dose modification.

TRIBUTE (Tarceva responses in conjunction with paclitaxel and carboplatin), a phase III trial however demonstrated no benefit of erlotinib except for in a subset of patients who were never smokers.

**Erlotinib for Pancreatic Cancer:**

Patients with advanced or metastatic pancreatic cancers were assigned to receive gemcitabine with erlotinib (n = 285) or with placebo (n = 284). OS was longer for erlotinib arm (HR, 0.82) with 1 year survival of 23% versus 17%. Median PFS was 3.75 months vs. 3.55 months (HR, 0.77) for erlotinib arm. Skin rash was associated with better disease control.

**Imatinib:**

Imatinib mesylate an oral TKI with the activity against BCR-ABL protein, c-KIT and platelet derived growth factor receptor (PDGFR). Imatinib has established its efficacy in chronic myeloid leukaemia and being also used in certain solid malignancies which express c-KIT.

**Imatinib in Advanced Gastrointestinal Stromal Tumour (GIST):**

GISTs are mesenchymal malignancies and arise from Cajal cells of intestinal wall. GISTs express KIT and PDGFR and are resistant to conventional chemotherapeutic agents. Role of radiation is not established yet. Survival is poor for metastatic GIST.

In a pilot study, 23 patients with high risk GIST were treated with imatinib in adjuvant setting after R0 resection. Comparison was made with 48 historical cases. After 40 months of follow-up, only 1 of 23 patients had recurrence as compare to 32 of 48 patients without treatment.

In a randomized study patients with advanced or metastatic GIST were assigned to receive imatinib at 400 mg/d (n = 473) or 400 mg twice a day (n = 473). In ITT analysis responses were almost equal for both doses with CR of 5% and PR for 45% - 48%. Estimated OS for 2 years was 69% and 74% for once and twice daily dose respectively. Dose modification, treatment discontinuation and AEs were more common for twice daily dose arm.

**Sunitinib:**

Sunitinib is an oral TKI with activity against VEGF and PDGFR.

**Sunitinib for Renal Cell Carcinoma (RCC):**

In a phase III trial patients with metastatic RCC were randomized to receive sunitinib (n = 375) or IFN (n = 375). ORR for sunitinib arm was 31% versus 6% (p<0.001), all were PR. Median PFS was 11 months for sunitinib and 5 months for IFN (Figure 4). Although median OS has not been reached in either arm but seems to be better in sunitinib arm. Grade 3 AEs in sunitinib arm were diarrhoea, vomiting and hand-foot syndrome.

**Sunitinib for Gastrointestinal Stromal Tumour (GIST):**

Patients with metastatic and imatinib resistant GIST were randomized to receive sunitinib (n = 207) or placebo (n = 102). In ITT analysis TTP was substantially lengthier for sunitinib (27.3 vs. 6.4 weeks, p=0.0001). PR was obtained for 7% patients while 58% had SD and 19% experienced PD. Major AEs were diarrhoea, fatigue, hand-foot syndrome and skin changes.
Sorafenib:

Sorafenib is also an oral TKI with activity against multiple TKs.

Sorafenib for Renal Cell Carcinoma:

Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), a phase III study enrolled patients with RCC to receive sorafenib (n = 451) or placebo (n = 452). Median PFS was 5.5 months for sorafenib and 2.8 months for placebo arm (p<0.001). Of patients in sorafenib arm 1 patient achieved CR while the PR and SD was seen in 10% and 74% respectively. No patient in placebo arm observed CR while PR and SD was achieved by 2% and 53% respectively. Major AEs including deaths were more common in sorafenib group including cardiac ischaemia, diarrhoea, hand-foot syndrome and fatigue.

Sorafenib for advanced Hepatocellular Carcinoma (HCC):

HCC is a common malignancy in Asia and Africa and most of the time is advanced and incurable. So far treatment options have not improved the OS remarkably and responses are poor with chemotherapy.

In Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP), a multicentre, placebo-controlled, randomized phase III trial accrued patients histologically proven and treatment naive HCC with Child-Pugh liver function class A. Patients were randomized to sorafenib (n = 299) and placebo (n = 303) arms. OS was improved by 44% for sorafenib arm (10.7 vs. 7.9 months, p = 0.0006). Disease control rates were also better for sorafenib as well (43% vs. 32%). None of patient from both groups achieved CR. AEs were diarrhoea, hand-foot syndrome and bleeding, liver dysfunction, weight loss and hypophosphataemia.

Conclusion

Modern management of cancer therapy has been revolutionised by the introduction of targeted agents, although not all of the agents have proven to be equally efficacious, there is a real interest generated in the oncology community to further develop on this form of relatively less toxic way to treat cancers.

References


