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Old disease, new targets. Part-II, haematological malignancies

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Abstract

In last two decades newer therapies in cancer treatment have emerged and have opened new horizons. New term of targeted therapy has emerged and for certain malignancies the paradigm has really changed after the introduction of these agents. We have learnt and have seen the outcome of some diseases after the addition of these monoclonal antibodies (MoABs) and tyrosine kinase inhibitors (TKIs).

Rituximab a MoAB against CD-20 has really paved its role in the treatment of B-cell lymphomas and become the sort of standard therapy. The TKIs are newer agents available in a pill form and have inhibited many pathways at cellular level which are necessary for cancer development. Imatinib has really changed the prognosis and outcome of chronic myeloid leukemia (CML) remarkably. For those patients who develop intolerance to imatinib or their disease became resistant to the imatinib the newer agents like dasatinib and nilotinib are second line options.

The major edge of these newer agents is more potency with low side-effect profile. The major concern remains the cost.

Introduction

Cancer treatment has been revolutionized by the identification of specific targets on cancer cells and henceforth the development of what is called the Targeted therapy. The concept of targeted therapy is derived from the idea of a "magic bullet," first elaborated by Paul Erlich in the late 1800s, when he described a chemical with the ability to specifically target microorganisms. In cancer treatment, they hold a promise of lesser toxicity and better treatment outcomes, which has been proven so far in lymphomas, leukemias and a list of solid tumours, ranging from breast to brain cancers. The toxic profile of many cancer drugs and greater understanding of the molecular biology involved in cancer evolution gradually paved the way for development of the targeted agents over the past half of the century, to quote an example, discovery of Philadelphia chromosome and subsequent availability of a targeted agent like imatinib for cure has virtually changed the outcome of patients with CML.

Of all targets at cellular levels the oldest known are hormone receptors, the estrogen and progesterone receptors expressed on breast tumors. Over the time targets like CD-20, CD-57, epidermal growth factor receptor (EGFR) family of receptors and the vascular endothelial growth factor (VEGEF) receptors have been identified and their link to development and dissemination of cancer have been confirmed. Tamoxifen an estrogen receptor modulator has established significant therapeutic effects in hormone positive breast cancers. Similarly, efficacy of trastuzumab, a monoclonal antibody against Her2 receptor (EGFR 2) on breast tumour cells has also been proven scientifically.

The Modern targeted therapy is broadly divided in two groups, The MoABs and the TKI. MoABs are specifically designed to attach with a receptor expressed on cell surface to inhibit the receptor associated actions, while the TKIs inhibit the tyrosine kinase dependent cascade of reaction that result in cancer cell proliferation.

Tyrosine Kinases (TK) are basically enzymes which act in transferring the phosphorus to polypeptides. A human genome contains 90 TKs and 43 TK like genes. Thus all TKs tightly regulate important cellular mechanisms like survival, motility, proliferation and differentiation. Tyrosine kinase receptor typically has a extracellular ligand binding site, a transmembrane link and an intracellular domain, allowing at least three targets to be available for a hit.

TKs are quiescent until a ligand binds to the receptor leading to activation of complicated interwoven orchestra of events in cytoplasm and the nucleus. As TKs are regulated at many levels so it is not surprising that dysregulation at many levels can lead to cancer development. These dysregulatory mechanisms usually get activated after chromosomal abnormalities like translocations and mutations. A dysregulation in the tyrosine kinase receptors may result in cancer cell growth, increased invasiveness and vascularity leading to dissemination, and in addition a trend towards decreased apoptosis, all contributing to disease progression.

TKIs help do the opposite, and hence control the
disease. The dysregulatory pathways can be inhibited at several levels like inhibition of catalytic activity, blocking the dimerization of receptors and binding of ligands, increased internalization of receptors and antibody mediated cytotoxicity.5

A review of the targeted agents currently approved for use in different cancer scenarios is presented here (Table).

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FDA Approval</th>
<th>Approved Indications</th>
<th>Side Effect Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>November 1997</td>
<td>Follicular Lymphoma, CD 20+ NHLs*, Rheumatoid Arthritis.</td>
<td>Anaphylaxis, B-Cell depletion, activation of viral infection, unexplained prolonged neutropenia.</td>
</tr>
<tr>
<td>Tositumomab</td>
<td>June 2003</td>
<td>Relapsed follicular Lymphoma.</td>
<td>Myelosupression, B-cell depletion, hypothyroidism, second cancers.</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>September 2007</td>
<td>B-Chronic Lymphocytic Leukaemia.</td>
<td>Myelosupression, severe or fatal bacterial infections, activation of viral infections.</td>
</tr>
<tr>
<td>Imatinib</td>
<td>May 2001</td>
<td>Philadelphia chromosome positive CML+, Relapsed or refractory Philadelphia chromosome positive ALL, Gastrointestinal stromal tumor, Dermatofibrosarcoma protuberans.</td>
<td>Myelosupression, edema, muscle crampes, diarrhea and nausea.</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>June 2006</td>
<td>Imatinib resistant or intolerant CML in chronic phase, accelerated phase or blast crisis.</td>
<td>Myelosupression, pleural effusion, diarrhea, peripheral edema, headache and disturbed liver function</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>October 2007</td>
<td>Imatinib resistant or intolerant CML in chronic phase or accelerated phase.</td>
<td>Myelosupression, deranged liver function tests and skin rash.</td>
</tr>
</tbody>
</table>

Table: Approved indications and side effect

Rituximab:

Rituximab is a MoAB against CD-20 antigen, which is expressed on mature B-lymphocytes. Rituximab exerts its antitumour activity through cell mediated cytotoxicity, increasing apoptosis and complement dependent cell lysis.6 Rituximab not only sensitize lymphoma cells to chemotherapy but also has synergistic activity.7

Rituximab for Non Hodgkin's Lymphomas (NHL):

A large randomized trial by GELA (Groupe d'Etude des Lymphomes de l'Adulte) established the role of rituximab in the therapy of DLBCL in elderly patients. Patients were randomized to receive rituximab with standard CHOP (R-CHOP, n=202) or CHOP (n=196). After 2 years of follow-up results favoured R-CHOP arm with event free survival (EFS, p <0.001) (Figure-1), over all survival (OS, p=0.007) (Figure-2) and complete responses (CR, p=0.005). Addition of rituximab also reduced the risk of death and time to treatment failure (TTF).8

MabThera International Trial (MInT), a randomized, multinational trial used R-CHOP or CHOP like chemotherapy in younger patients diagnosed with DLBCL. Patients were randomized to receive rituximab with CHOP like chemotherapy (n = 413) and chemotherapy alone (n = 411). With median follow-up of 34 months EFS was 20% higher for rituximab arm (p<0.001). Progression free survival (PFS, p<0.001) and OS 93% vs. 84% (p < 0.0001) also favoured combination therapy.9

Figure-1: Event-free Survival among 399 Patients Assigned to Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) or with CHOP plus Rituximab. (With permission from Ref. No. 8).

NHL* = Non Hodgkins Lymphoma, CML+ = Chronic Myeloid Leukemia (URL http://www.cancer.gov/cancertopics)
Follicular lymphoma and mantle cell lymphoma (MCL) are well known for recurrences and good initial responses to chemotherapy.

Chemotherapy naive patients with stage III or IV follicular lymphoma were treated with R-CVP or CVP alone. Responses were significantly better with R-CVP [CR 41% vs. 10% (p<0.0001), TTF p<0.0001].

German Low-Grade Lymphoma Study Group (GLSG) compared R-CHOP and CHOP in patients with advanced stage follicular lymphoma. With median follow-up of 18 months significant trends were observed in regard of TTF (p <0.001), longer remission (p <0.001), treatment free interval (p=0.001) and OS (p=.016).

**Maintenance rituximab for Non Hodgkins Lymphomas:**

Intergroup trial evaluated the role of maintenance rituximab in older patients (>60 years) after induction therapy with CHOP and R-CHOP. Patients treated with R-CHOP had better failure free survival (FFS) of 53% vs. 46% (p = 0.009). Beneficial effect of maintenance rituximab was more evident in patients who received CHOP (p = 0.0004) vs. R-CHOP (p = 0.81) as induction therapy. Maintenance rituximab did not improve the OS.11

GLSG performed a trial on patients with refractory/relapsed follicular lymphoma and MCL. Patients were randomized to receive fludarabine, cyclophosphamide, mitoxantrone (FCM) or R-FCM. Over all response rates (ORR = 79% vs. 58% p = 0.01) and CR (33% vs. 13%; p= 0.005) were better for R-FCM group, for both follicular lymphoma and MCL.12 Responding patients were then assigned to maintenance rituximab vs. observation. Patients with follicular lymphoma, who received maintenance rituximab had prolonged duration of response with estimated 26 months (p= 0.035). For patients with MCL difference of 2 months was noted (p= 0.049). More patients will be alive in maintenance arm at 3 years (77% vs. 57%, p= 0.1).13

In multcenter, intergroup trial patients with resistant-relapsed follicular lymphoma were randomized to R-CHOP (n=234) and CHOP (n=231) arms. ORR (85.1% vs. 72.3%) and CR (29.5% vs. 15.6%, p = 0.001) were better for patients assigned to R-CHOP arm. The responders were then randomized to 2 years of maintenance rituximab (n=167) or observation (n = 167). Median PFS of 51.5 months vs. 14.9 months was observed for patients on maintenance rituximab arm (p = 0.001). Maintenance rituximab improved median PFS to 42.2 months vs. 11.6 months after induction with CHOP [hazard ratio (HR), 0.30; p = 0.001] and to 51.8 months vs. 23 months after induction with R-CHOP (HR, 0.54; p = 0.004). Three years OS of 85.1% and 77.1% was demonstrated for maintenance rituximab and observation groups respectively.14

**Rituximab for Chronic Lymphocytic Leukaemia (CLL):**

Most common haematological malignancy in adults is CLL. Combination of rituximab and fludarabine has better responses as compare to fludarabine alone.

In a retrospective analysis of 2 studies, performed by Cancer and Leukaemia Group B (CALGB 9712 and CALGB 9011) better PFS and OS were seen for patients who were treated with rituximab and fludarabine. Patients treated with combination therapy had significant CR (0.38 vs. 0.20, p = 0.002), ORR (0.84 vs. 0.63, p = 0.0003) and OS (p = 0.003).15

Keating et al used combination of rituximab, fludarabine and cyclophosphamide as initial therapy in patients with CLL. Out of 224 treated patients, 156 attained CR (70%), 23 (10%) achieved nodular PR (NPR), and PR in 34 (15%) patients. Of 156 patients with CR, 154 were alive till July 2003. Advanced stage, high leukocyte counts, thrombocytopenia, increased β-2 microglobulin levels, enlarged spleen, bone marrow cellularity of >50% and old age were the confounding factors for poor response.16

**Rituximab for Graft versus Host Disease (GVHD):**

Around one third of long term survivors of allogeneic stem cell therapy (SCT), succumb to chronic GVHD. One of the postulated underlying mechanisms for chronic GVHD is immune mediated donor T cell reactions, but depletion of T cells did not translate to decreased
incidence of chronic GVHD. Increasing evidence is suggesting that B cells have some underlying role in pathophysiology for GVHD.

Rituximab was administered to 21 patients with steroid refractory chronic GVHD. Responses were seen in 12 (70%) patients with CR for 2 patients. Significant decrease (p= 0.001) in steroid dose was observed. Improvement in cutaneous and musculoskeletal symptoms was observed at the end of one year.17

With these encouraging results rituximab has changed the paradigm in treatment of B cell NHLs. Ever increasing indications are coming up and rituximab is being used for immune mediated thrombocytopenic purpura, autoimmune haemolytic anaemia, rheumatoid arthritis and pemphigus vulgaris.6

**Tositumomab:**

Tositumomab, a murine IgG2a antibody which when labeled with radioactive Iodine-131; attacks surface CD-20 receptors on B-cells. It further improves the responses attained with rituximab by virtue of having a radioactive substance (I 131) attached to it.

Improved responses may be because of addition of radiation effects, which not only kill the cell it is attached with but also destroy the surrounding cells; together with the cytotoxic and apoptosis properties of the antibody. 131I tositumomab exerts its effects with antibody-mediated actions of tositumomab and ionizing effects of I-131. Because decaying iodine-131 releases short range ß particles and ß rays, it is possible to calculate exact delivery dose to the cancer cells and minimizing adverse effects.18

In a phase III, multicenter study, patients with refractory low grade B-cell NHL received single dose of 131I tositumomab. Patients had to receive chemotherapy with proven efficacy in NHL, before getting the radio labeled therapy. Responses were compared between the responses obtained after last chemotherapy and after iodine labeled therapy. Better responses were observed after 131I tositumomab than after last chemotherapy (65% vs. 28%; p = 0.001). CR (20% vs. 3%) and median PFS (8.4 months vs 6.3 months) were significantly better for patients treated with 131I tositumomab as compared to chemotherapy.18

South West Oncology Group started a phase II trial to assess the efficacy and safety of 131I tositumomab after induction therapy with 6 cycles of CHOP in patients with newly diagnosed follicular lymphoma. More than two third of patients had stage IV disease. Of 90 eligible patients, 77 received full protocol therapy. CR achieved by 49 (54%) patients, CRu in 11 (12%) and PR in 21 (23%) after completion of planned therapy with CHOP plus 131I tositumomab. Objective response of 90% was obtained. Four patients (9%) with CRu after CHOP achieved CR with 131I tositumomab, and 23 (49%) patients attained CRu or CR after radioactive therapy. Estimated 2 years PFS and OS were 81% and 97% respectively.19

**Alemtuzumab:**

Alemtuzumab is a humanized monoclonal antibody with activity against CD-52 expressing lymphocytes. CD-52 antigen is expressed on almost every B and T lymphocyte, normal or malignant and is also present on monocytes and macrophages. Alemtuzumab has been approved for fludarabine refractory B-CLL.20 After binding specifically with CD-52, it exerts its effects through complement activation apoptosis and antibody dependant cell mediated toxicity.20-22

**Alemtuzumab for Chronic Lymphocytic Leukaemia (CLL):**

Patients with CLL refractory to fludarabine were treated with alemtuzumab in a phase II trial. A total of 93 patients were enrolled and after 12 weeks of therapy, ORR of 33% (CR = 2% and PR = 31%) was achieved. Median survival of 16 months and median response duration of 8.7 months were observed. Twenty five patients, experienced severe infection with sepsis in 14 patients. Support with colony stimulating growth factor was required by 35% patients.23

In a randomized, multicenter, phase III trial, patients were randomized to receive alemtuzumab (n= 149) or chlorambucil (n=148) as first line therapy for CLL. ORR (83.2% vs. 55.4%, p = 0.0001), CR (24.2% vs. 2%, p = 0.0001), minimal residual disease (MRD, 7.4% vs. 0%, p = 0.0008), time to start 2nd therapy (88 weeks vs. 36 weeks) favored alemtuzumab. PFS was also better with alemtuzumab (p= 0.0001). OS has not been reached for both the arms after a median follow-up of 2 years. Infusion related AEs, haematological toxicities and more CMV activation events were seen with alemtuzumab.24

Moreton P et al assessed the effect of elimination of MRD after treatment with alemtuzumab on survival. Of 91, majority of patients were heavily pretreated including purine analogues. ORR was achieved 53% patients with CR for 35% (MRD+ = 15% and MRD- = 20%) and PR for 19%. Of 18 patients who achieved MRD- remission, 13 had no lymphadenopathy on presentation and 16 (88%) were alive with a median follow-up of 36 months. Treatment free survival (TFS) and OS were substantially higher for patients who attained MRD- CR.21

To assess the effect of combination of alemtuzumab and rituximab, 48 patients with relapsed/refractory lymphoid malignancies were treated. Bone marrow was
involved in 44 patients and 32 had CLL. Responses were observed in 52% patients with CR for 8%, nodular PR for 4% and PR for 40%. SD or progression was seen in remaining 23 patients. Median OS for responding patients was 11 months compared to 6 months for non responders.25

Alemtuzumab for Mycosis Fungoides and Sézary Syndrome (MF/SS):

Mycosis fungoides and Sézary syndrome are one of common cutaneous lymphomas, usually with indolent course. But these may infiltrate peripheral blood, lymph nodes and other viscera. Patients with MF/SS usually die of septicemia secondary to suppressed cell mediated immunity and skin disruption.

In a phase II trial, 22 patients with relapsed MF/SS received alemtuzumab for 12 weeks. CR was achieved for 7 patients, PR for 5, SD for 3 and progressive disease (PD) was seen in 7 patients. Median TTF was 12 months for responding patients.22

Imatinib:

Imatinib mesylate a TKI inhibits multiple TKs, including ABL, BCR-ABL, platelet-derived growth factor receptor (PDGFR), and c-kit. Imatinib induces apoptosis of BCR-ABL+ cells as it halts the downstream signals for growth by preventing the phosphorylation of BCR-ABL. FDA approved imatinib in May 2001 for the treatment of CML.

Imatinib in Chronic Myeloid Leukaemia (CML):

CML is a myeloproliferative disorder which is characterized by clonal abnormality of haematopoietic cells after a balanced translocation of chromosomes 9 and 22, [t(9;22)(q34;q11)] also known as Philadelphia (Ph) chromosome. Most of the times, patients get diagnosed with high leucocyte counts. CML has chronic phase (CML-CP), accelerated phase (CML-AP) and an aggressive blast crisis. The median survival for CML-CP was 3-5 years and 6 months for blast crisis before the introduction of imatinib. Hydroxyurea, interferon, cytarabine and allogenic SCT were the treatment options. Patients with complete cytogenetic response (CCyR) had higher survival as compare to patients who do not attain that.26

The IRIS (International Randomized Study of Interferon and STI571) trial is a randomized, multicentre, phase III trial, which compared the efficacy of imatinib with interferon alfa and low dose cytarabine. A total of 1106 (553 in each group) patients were randomized to receive imatinib at 400 mg orally daily or interferon alfa with subcutaneous cytarabine. Primary end point was progression and secondary endpoint was complete haematologic response (CHR). With the median follow-up of 19 months more patients in imatinib group achieved CHR (95.3% vs. 55.5%, p<0.001) and major cytogenic response (MCyR, 85.2% vs. 22.1%, p<0.001). PFS (92.1% vs. 73.5%, p<0.001) and estimated OS (97.2% vs. 95.1%, p = 0.16) favoured imatinib therapy.27

After a median follow-up of 5 years of this study, 69% of patients in imatinib group were on treatment while only 3% in combination therapy group. More patients in immunotherapy arm crossed over to imatinib arm (65% vs. 3%). The most common reason being the intolerance to therapy. MCyR were observed by 89% patients while 82% patients achieved CCyR (Figure-3). Patients with CCyR at

Imatinib in Acute Lymphocytic Leukaemia (ALL):

At 12 months after the initiation of imatinib, the estimated rates of having a response were as follows: complete hematologic response, 96%; major cytogenic response, 85%; and complete cytogenetic response, 69%. At 60 months, the respective rates were 98%, 92%, and 87%. Data for patients who discontinued imatinib for reasons other than progression and who did not have an adequate response were censored at the last follow-up visit. Data for patients who did not have an adequate response and who stopped imatinib because of progression were censored at maximum follow-up. (With permission from Ref: # 28).

12 months in imatinib group (97%), did not progress to AP or blast crisis after 5 years of median follow-up. Estimated 5 year survival was 89% for imatinib arm. The most common AEs were edema (60%), muscle cramps (49%), diarrhoea (45%), nausea (50%), grade 3 or more neutropenia (17%), thrombocytopenia (9%) and anaemia (4%).28

Imatinib in Acute Lymphocytic Leukaemia (ALL):

Adult patients with ALL have poor out-come even with SCT as compare to children and adolescence. The reasons are drug resistance, poor compliance and acceptance and molecular abnormalities. BCR-ABL fusion has been observed in 3% of children diagnosed with ALL.

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and increases to 20% for adults and even >50% in patients >50 years.29

Adult patients with Ph+ ALL entered a phase II trial and were treated with chemotherapy and imatinib. Imatinib was added to consolidation chemotherapy before proceeding to allo- or autologous SCT. Of 45 patients 43 patients achieved CR. OS of 65% and DFS of 51% were observed at median follow-up of 18 months. Advanced age was associated with poor OS.30

Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) enrolled 30 elderly patients with diagnosis of Ph+ ALL in a phase II trial. Patients were treated with imatinib and steroids. After 45 days of therapy all patients achieved CHR with median duration of response of 8 months and median survival of 20 months.31

**Imatinib in Acute Myelogenous Leukaemia (AML):**

The prognosis of AML depends on age, karyotype and post-induction regimen. After treatment with daunorubicin and cytarabine chemotherapy, 5 year OS is 40% for patients <60 years and only 6%-15% for older patients. Allogenic SCT is an option for patients with refractory AML but because of procedure associated morbidity and limitation of available matched donor; most patients are not eligible for this treatment. For the maintenance of normal haematopoiesis, c-kit plays an important role. c-kit activity has been seen in certain human malignancies including AML. Besides other targets imatinib inhibits c-kit associated signals as well.

In an open label, phase II study patients with refractory or newly diagnosed AML were treated with imatinib only. Of 21 patients 2 achieved CHR, 1 had no evidence of leukaemia and 2 patients achieved sustained minor response.32

Imatinib is standard of care for patients with the diagnosis of CML. It has established its role in gastrointestinal stromal tumour (GIST) as well.

**Dasatinib:**

Despite on imatinib some patients with CML develop resistance due to new mutations or they just cannot tolerate imatinib. Dasatinib is another oral ABL kinase inhibitor. Dasatinib has the property of binding active and inactive domain and it also has activity for imatinib resistant domains.

In a phase I, open label study 40 patients with CML-CP, 11 with CML-AP, 23 with myeloid blast crisis, and 10 with lymphoid blast crisis or Ph+ ALL were registered to receive dasatinib. Of 40 patients with CML-CP, 92% attained CHR with 45% MCyR. For patients with CML-AP or blast crisis or ALL the CHR was seen in 70%. Grade 3 or 4 myelosupresion was common AEs requiring dose reduction or treatment interruption. Other AEs were pleural effusion, diarrhoea, peripheral edema, headache and disturbed liver function.33

In a multinational, phase II trial, 107 patients with imatinib resistant or intolerant CML-AP were treated with dasasatinib at 70 mg twice daily. Primary end point of the study was the major and over all haematologic responses (OHR). After 8 months of follow-up, 69 patients achieved major haematologic response with CHR for 42 patients. OHRs were observed in 81% patients and MCyR in 33% patients. Pleural effusion developed in 25 patients. Grades 3 or 4 pancytopenia were present at the start of therapy in some patients and almost every patient observed some degree of cytopenias while on therapy.34

**Nilotinib:**

Nilotinib is a new TKI which is more potent than imatinib against CML. It inhibits competitively the binding site of BCR-ABL with 20-50 times higher activity than imatinib and is also active in patients with imatinib resistant CML.

In a phase I dose escalation study, 119 patients imatinib resistant CML or ALL were registered. Patients were treated with escalating doses of nilotinib starting from 50 mg once daily to 600 mg twice daily. Of all 33 patients with blast phase CML, 13 patients achieved haematologic response with MCyR for 6 patients. Among 46 patients with CML-AP, 33 had haematologic response with MCyR for 9 patients and of 17 patients with CML-CP, 11 achieved CHR and 6 patients attained CCyR. Of 10 patients with Ph+ ALL, 1 observed partial haematologic response and 1 among 3 patients with Ph+ ALL with persistent molecular signs attained complete molecular response. Grade 3-4 thrombocytopenia, neutropenia and deranged liver function tests were major toxicites.35

**Conclusion**

The treatment paradigms in cancer therapy have been redefined by the introduction of targeted therapies. Their fair toxicity profile, ease of administration, molecular basis of action and proven efficacy in phase III trials make them an attractive choice. Their cost however remains there downside. In developing countries there would be an imperative need to use these agents judiciously and properly by identifying the patient population that might benefit from this form of therapy.

Increasing understanding of molecular basis of cancer promises greater discoveries in the treatment of cancer and perhaps finer targeted therapies as well. Indeed
with such a rapid advance the future of patient tailored therapy does not look like a distant dream.

References


