The advent of hybridoma technology by Kohler and Milstein (1) ushered in the era of production of monoclonal antibodies (MAbs) in large quantities for routine clinical use. The knowledge that specific tumors overexpress specific antigens has led to the use of these monoclonal antibodies in oncology. Monoclonal antibodies have been used in diagnostics as well as therapeutics. This article will focus on therapeutics.

The initial experiences with first generation MAbs were not very encouraging. This was because these initial MAbs were murine in origin and the humans responded with human antimouse antibodies (HAMA) that antagonised these therapeutic MAbs. This has been overcome by modifying the structure of the murine antibodies and through chimeric ones we now have fully humanised MAbs.

A tumor cell has an advantage over a normal cell in form of it being resistant to chemotherapy / radiotherapy, increased survival by altered apoptotic pathway, having a metastatic potential and able to induce angiogenesis. This is possible due to the increased signaling of the signal transduction cascade. This pathway is as shown in fig 1. This pathway is over stimulated because of a number of substances that are also produced by the tumor which act as autocrine, paracrine and even endocrine signals to drive to tumor cells.

MAbs act by several mechanism some of the well characterized are,

- Binding to receptors and blocking downstream signaling.
- Downregulation of receptors
- Immunomodulation
- Antibody dependant cytotoxicity (ADCC)
- Complement dependant cytotoxicity (CDCC)

Some obstacles to exist to efficient MAb activity, a few of these are,

- Impaired MAb distribution and delivery to tumor sites, (may be size related)
- Inadequate trafficking of effector cells to tumor
- Intratumoral and intertumoral heterogeneity.
- Shed or internalized receptor targets
- Insufficient tumor specificity of tumor antigens.

Monoclonal antibodies can be classified as,

- Unconjugated
- Conjugated, here the conjugates could be toxins, radio isotopes, immunocytokines etc.

They may also be classified as,

- Targeting the tumor pathways.
- Targeting non-tumor pathways.

The only MAb targeting the non tumor pathway that is approved for clinical use is Bevacizumab which targets the vascular endothelial growth factor (VEGF) and blocks angiogenesis that is so essential for the progression of the tumor.

**UNCONJUGATED MABS**

*Against solid tumors*

**TRASTUZUMAB**

Breast cancer is one of the major cancers worldwide. Nearly 25-30% of these cancers overexpression HER-2 receptor, a member
of the EGFR family. This phenotype is associated with aggressive behaviour of the tumor, increase incidence of metastasis, recurrence and poor survival.

Trastuzumab is a chimeric MAb developed to target (TZM) this HER-2 receptor. This is the first MAb to have been approved for clinical use in cancer.

Early phase II studies in metastatic breast cancer showed responses of 11-16% thus showing its activity as a single agent in HER-2 overexpressing breast cancers. (2)

TZM, in combination with a taxane regime has shown a response rate of 57.3% as against 25% with only chemotherapy in the registrasion phase III study. (3)

With such impressive results in metastatic disease TZM logically reached its role in the adjuvant breast cancer. In multi phase III trials the use of TZM showed approximately 50% reduction in recurrence after 1 year. A further two year follow-up has demonstrated better disease free survival (DFS) and overall survival (OS) as compared to observation alone. (4)

Myocardial dysfunction is seen with TZM but is usually reversible. This effect is compounded by concurrent use of anthracyclines and hence the combination is to be avoided.

There is emerging data of its use in other HER2 over expressing tumors such as lung and stomach.

CETUXIMAB

This is a chimeric 1gG1 MAb that binds to EGFR or HER-1. Its binding affinity is ten fold higher than the natural ligands EGF and TGF-α. This binding leads to inhibition of the downstream tyrosine kinase activation.

It was evaluated in a phase II study of 329 patients of colorectal cancer in combination with irinotecan and showed an increase in overall response (5). It is now approved in first and second line metastatic colorectal cancer with chemotherapy.

Cetuximab is also important in squamous cell Head and neck cancers along with radiotherapy.

Non small cell lung cancer is another tumor that has recently shown to benefit when used along with chemotherapy.

A bothersome side effect has been an acniform rash but this seems to correlate with responses. It can also cause hypomagnesemia.

NIMUTUZUMAB

Is another EGFR targeting MAb. This is a humanized MAb and unlike cetuximab has very little side effects with no rash and hypomagnesemia. It is being produced in India. It is now approved for head and neck cancers along with chemo and radiotherapy. (6),(7)

Initial trials in Non-small cell lung cancer and glioma have shown promise when used in combination with chemotherapy.

PANITUZUMAB

This is a fully humanize 1gG2 MAb against EGFR. It has a higher binding affinity than cetuximab.

A Phase III study of 463 patients with metastatic colorectal cancer compared panitumumab plus best supportive care (BSC) to BSC alone. A partial response rate of 8% and a stable disease of 28% was seen with panitumumab as against a 10% stable disease rate seen with BSC alone, along with a statistically significant progression free rate.

BEVACIZUMAB

Is a humanized MAb targeting VEGF. It is approved for first line use in metastatic colorectal and Non Small cell lung cancer. A survival advantage is seen in both these cancers.

Activity has also been demonstrated in metastatic renal cell cancer, gliomab and Hepatocellular carcinoma.

Against Hemotologic Malignancies

RITUXIMAB

This is a MAb against CD 20 antigen. It is a humanized MAb. Its efficacy as a single agent was demonstrated in a phase II study of previously treated B-Cell follicular lymphomas showing a response rate of 50%. Another Phase II study evaluating it in relapsed or refractory diffuse large B Cell lymphoma, mantle cell lymphoma showed a response rate of 31%. (9)

The combination of this MAb with chemotherapy of cyclophosphamide, adriyain, vincristine and prednisolone (R-CHOP) in 40 patients of low-grade or follicular lymphoma resulted in an overall response of 95% with a 55% complete response and 40% partial response. A high percentage who were positive for bcl-2 translocation became negative by PCR assay after treatment. (10)

It is now shown good activity in large cell lymphomas, Multiple myeloma, Hodgkins lymphoma also.

ALEMTUZUMAB

This MAb targets CD 52 antigen, overexpressed on T and B lymphocytes. It has shown activity in chronic lymphatic leukemia, promylocytic leukemia and non-Hodgkins lymphoma.

CONCLUSION

MAb therapy in the last two and a half decades has made tremendous progress. The clear understanding of cell biology has let this field of immunotherapeutics as a new vista for treating several malignancies. It is projected that in the coming years the progress in biologic therapy (including immunotherapy with MAbs) will outbeat the usage of other cancer therapy modalities such as chemotherapy, hormone therapy etc. MAb therapy from being a science fiction has today become a true reality.
REFERENCES


4. Smith I, Procter M, Gelber RD et al. Two year follow up of trastuzumab after chemotherapy in HER-2 positive breast cancer: a randomized controlled trial.


