Breakout 3 Report:

Apoptosis Induction and Immunotherapy

Conclusions

1. Several new agents which target Bcl-2 family are becoming available.

2. Key drugs appeared to be :

   (1) ABT-737 Currently not effective against tumors with high levels of Mcl-1 but Mcl-1 may be downregulated by using other agents such as sorafenib or GSK-3b inhibitors..

   (2) TW37 targets all the antiapoptotic proteins. Studies in NOD/SCID s have not shown major toxicity to normal tissue.

   (3) Selectivity of Obatoclax (GX015-070) not certain. Mode of action of Genasense also not clear.

   (4) New agents against IAP 1 and 2 showing promise. Release of TNFa in cells causes death.

3. General concerns about the effect of signaling pathway inhibitors on immune responses should be the focus of future studies.

- In animal models
- In vitro on immune cells (sorafenib known to inhibit DC function)
- In clinical trials- (velcade- proteosomal inhibitor- In inhibits T cells

4. Futures studies should be to obtain information on the effect of these agents on the immune response.

5. Timing of administration of signaling pathway inhibitors maybe critical. Different forms of immunotherapy may be more effective after use of antiapoptotic drugs or signal pathway inhibitors.

6. Mode of death of cancer cells may be important in the generation of subsequent immune responses or in providing growth factors for tumor growth.

   No strong consensus reached on this point.

7. It was not always clear what the mode of tumor death was by immunotherapy and could be made a subject of future studies.

8. It was suggested that treating patients with antibodies to high mobility group protein 1 after chemotherapy may reduce inflammation and inhibit tumor growth.

9. An effective form of treatment may be immunotherapy combined with a MEK inhibitor plus a broad spectrum anti-apoptotic inhibitor such as TW37, or ABT737 combined with an inhibitor of mcl-1.