Modelling Cancer Immunotherapy

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Cancer is a multi-faceted disease that is well characterised by the “Hall Marks Of Cancer” (Hanahan & Weinberg, 2011). An important hallmark that has emerged is the ability of solid tumours to evade detection by the host’s immune system. This has resulted in the discovery and development of new anti-cancer treatments targeted to enable the immune system to attack the tumour based upon the cancer immunity cycle (Chen & Mellman, 2013). The approaches range from vaccines to targeting tumour cells ability to inhibit local T-cell response. This former approach aims to reset the immune system whereby the immune system acquires and retains the ability to “see” the tumour and effectively kill tumour cells. Some of these approaches have seen encouraging results in the clinic: although only a minority of patients respond to these agents those that do see their tumours disappear with few cases of relapse observed.

Given these encouraging results for these Immunotherapy agents (Hence forth IO for Immuno- Oncology) treatments, clinical investigations are expanding to combine with established standards of care (SoCs) as well as novel targeted small molecule inhibitors. These small molecules take advantage of other aspects of the hallmarks of cancer by inhibiting aspects of cell proliferation, survival and signalling. The best way to dose these combinations results in a number of questions.

The immune system is complex, however there are a number of useful publications as primers for modellers (Hawse & Morel, 2014).

There are a number of example models in the literature

1. Interaction of tumour and T-cells (Robertson-Tessi, El-Kareh, & Goriely, 2012)(dePillis, Eladdadi, & Radunskaya, 2014)
2. Determining optimal schedules (Cappuccio, Antonio ; Castiglione, Filippo ; Piccoli, 2007)(Piccoli & Castiglione, 2006)
3. The role of cytokines (Cappuccio, Elishmereni, & Agur, 2006)
4. Integration of multiple models into one system (Palsson et al., 2013)

Questions

Based upon the above background the following is a summary of the questions surrounding the best use of these IO agents in combination with other treatments. It is suggested to consider some case studies of combinations in the literature as motivating examples (Cooper, Reuben, Austin-Breneman, & Wargo, 2015) (Twyman-SaintVictor et al., 2015)(Parra-Guillen, Berraondo, Grenier, Ribba, & Troconiz, 2013)(Kakavand et al., 2015). It is clear that the immune system has a threshold like behaviour whereby sufficient stimulus is required before it decides to act. For combinations of immune therapies and other treatments this will be dependent upon a number of factors, importantly what the SoC or small molecule inhibitor “does” to cancer cells and the immune system.

1. What is the optimal relative sequencing of agents (immune therapy + other anti-cancer treatments) with different mechanisms? Some topics to consider/issues to consider in order of importance
    1. Short sharp burst of cell kill vs longer low level for the “targeted” or “kinase inhibitor” type drugs. How important is it to increase the antigenicity of the tumour by killing cells with a targeted agent or chemotherapy versus reducing proliferation of cells (a maintenance effect)? This situation is analogous to a vaccine.
    2. Some small molecules kill or inhibit T-cells: What would the impact of a preferential effect on T-regs vs T-effector cells?
    3. Would a decreased dose of immune therapy be adequate in the presence of small molecule? Or shorter duration of treatment?

4. How long do we have to do treat for: or how would we know when enough is enough? The hypothesis behind immune therapy is to reset the immune system in the tumour – therefore continued treatment should not be necessary.

2. Impact of model assumptions
3. Key data/experiments to inform model?

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