Development of quantitative approaches for combination therapy optimization

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Problem overview

With the emergence of exciting new treatment options for cancer, the space of combination therapies still remains largely unexplored. Development of quantitative methods to guide development of combination therapies has the potential to greatly impact patient outcomes in the coming years.

Background

What do we now know about most solid tumors?

Tumors that are most difficult to eradicate are highly genetically heterogeneous, and they keep mutating over time. Therefore, administration of traditional chemotherapy on the MTD (maximal tolerated dose) regimen results in killing of the therapy-sensitive clones, leaving behind the therapy-resistant population.

Furthermore, transformed malignant cancer cell do not make up the entire tumor. In fact, a large portion of the tumor is transformed stromal cells, which support tumor growth. They engage and modify their microenvironment through changing the pH, transforming fibroblasts to induce production of angiogenesis stimulators, effectively creating a niche for themselves within the tissue.

Therefore, a more systemic approach to tumor eradiation is more likely to be successful.

Standard treatment modalities involve cytotoxic therapies that aim to increase cancer cell mortality (chemotherapy, radiation therapy, etc.), and approaches that aim to augment the body's natural defense mechanisms (i.e., immunotherapy). Finding an efficacious combination of these approaches has high potential to create a synergistic effect and improve treatment outcome.

Chemotherapy

Cytotoxic chemotherapy acts by interfering with cell growth, or inducing cell death of dividing cells, often through interfering with different stages of the cell cycle. Standard protocol for cancer treatment is called MTD, which stands for 'maximum tolerated dose'. It involves administering the highest dose of the chemotherapeutic agent that can be tolerated by the patient; it requires prolonged intervals between treatments to allow time and opportunity for normal tissues to recover and repair themselves – they tend to do so faster than cancer cells, since they typically are not dividing as actively.

This approach was derived from success in treating acute lymphoblastic leukemia (ALL) in children, a rare case when the cancer clone can be completely eradicated (1). It was first established in 1960s, before there was a realization that 1) most tumors are genetically heterogeneous (this realization came with the explosion of the field of molecular biology in the 1970s) and 2) most complex and difficult to treat tumors engage and modify their environment.

Therefore, MTD works best for more genetically homogeneous tumors (i.e. ALL, testicular cancer, Hodgkin disease, B cell non-Hodgkin lymphomas) but not for complex cancers, such as sarcomas, breast, pancreatic and lung cancer.

Metronomic chemotherapy

With some anticancer agents, a dose that is needed to inflict significant damage to the supporting cells of the tumor microenvironment is so low that tumor cells can be spared. All tumor cells depend on the stromal compartment for pro-angiogenic signals that recruit the blood vessels needed to access oxygen and nutrients. Consequently, chemotherapeutic drug doses and schedules that selectively target these and other critical cells within the tumor microenvironment can inflict severe damage on both resistant and sensitive tumor cell clones. This can weaken the entire tumor cell population without specifically selecting for resistant clones.

One approach that allows doing this involves administration of same chemotherapeutic drugs used in MTD but on a different schedule, giving the patients lower doses at more frequent time intervals. This approach is called “metronomic” chemotherapy, and it has numerous advantages. It is much easier on patients, improving patient quality of life; it allows repurposing of drugs, making it cheaper, and most importantly, it has important therapeutic benefits compared to the standard MTD approach, which includes preservation and augmentation of anti-tumor immunity, decreased angiogenesis, and potential for decreased therapeutic resistance.

The functionality of the immune system can be compromised by high dose chemotherapy as immune cells can be ablated by the cytotoxic drugs, preventing them from pursuing therapy-resistant cancer cells. However, metronomically administered chemotherapy can target and thus reduce the numbers of immunosuppressive regulatory T cells (Tregs). It can also promote maturation of antigen presenting cells, and most importantly, improve activation and functionality of key cytotoxic immune cells, particularly the natural killer (NK) cells of the innate immune response, and CD8+T cells of the adaptive arm of the immune system.

Specifically, Doloff and Waxman demonstrated that administration of metronomic cyclophosphamide every six days (Q6day cycle) resulted in significant recruitment and activation of natural killer (NK) cells, dendritic cells and macrophages, a response that was accompanied by dramatic regression of implanted glioma xenographs. More frequent administration of cyclophosphamide inflicted severe damage on NK cells themselves, while Q9day and Q12day schedule eventually resulted in tumor escape. Similar results were obtained for increasing activation and functionality of CD8+T cells.

However, finding the right timing is not sufficient – the authors also showed that the efficacy metronomic scheduling of chemotherapy for activation of the anti-tumor immune response was both **time- and dose-dependent**. Reduction in dose caused insufficient immune stimulation, while a dose that was too high increased immune cell mortality.

Therefore, appropriate timing and dosing schedule might dramatically improve disease outcome by both engaging and protecting anti-tumor immune responses, but finding this sweet spot for different cancer types still remains a challenge.

Immunotherapies

One of the most promising recent advancement in immunotherapy are checkpoint inhibitors, which target the mechanisms that regulate immune cell activation and cytotoxic function against self-antigens

as a protection against auto-immune disease. Alleviating some degree of checkpoint activity has been shown to significantly augment immune responses, leading to improved outcomes in cancer patients. The two currently most well-researched targets involve inhibition either of the cytotoxic T-lymphocyte antigen-4 (CTLA-4) cell surface receptor, which improve activation of the anti-tumor response, and the programmed cell death-1 (PD-1) surface receptor, or the corresponding soluble PD-L1 or PD-L2 ligands, which prevent T cell exhaustion and allow prolonged survival of anti-tumor immune cells.

There have been attempts at combining these two types of immunotherapy, which have shown promise. A combination of metronomic chemotherapy and immunotherapies might also be of interest.

Data and information that are available to help address the problem

Experimental

Chemotherapy: Experimental results from the lab of David Waxman at Boston University have shown efficacy of metronomic chemotherapy in mouse models, and have highlighted the importance of appropriate **timing and dosing** to achieve an optimal immune cell activation.

Immunotherapy: Research done by Jedd Wolchok at Memorial Sloan Kettering Cancer Center, among others, has shown that there may exist a synergy in combining CTLA4 and PD-1 checkpoint inhibitors. However, no quantitative approaches to determine optimal doses and combinations yet exist.

Mathematical

Chemotherapy: Recent work by Chakrabarti and Michor (2017), as well as Ciccolini et al. (2017), among others, has highlighted the effect of lower dose higher frequency chemotherapy on improved tumor eradication. The added effect on the immune cells still remains to be evaluated.

Immunotherapy: Modeling work has been done on combinations of chemotherapy and radiotherapy, see for instance the report from 2015 meeting at Alderly Edge (cited below), as well as in work by Serre et al. (2016), among others. Some work on modeling combinations of chemo and immunotherapy has been done by Rösch et al. (2015), Pang et al. (2016), among others. The authors have started exploring the dual effect of chemotherapy in both augmenting and suppressing the immune response, and the potential of immunotherapy to augment the anti-tumor effect.

Questions to explore during the meeting

While some modeling work on combination of immunotherapy and chemotherapy has been done, the question of finding an optimal combination with respect to timing and dosing still remains open.

1) How can we administer chemotherapy in such a way as to also augment the immune response (metronomic schedule)? How do we optimize the effect to augment effector T cells and diminish regulatory T cells, both of which would be affected by the therapy in addition to cancer cells themselves?
2) At which point should we administer immunotherapy to augment the effects achieved by metronomic chemotherapy (i.e., preventing T cell exhaustion or increasing activation)?
3) Can we find an algorithm for making combination therapy predictions given PK-PD properties of the drug(s) and any information about the tumor that can be obtained from a biopsy?
4) How can we determine if the effect of combination therapies is additive or synergistic?

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Experimental

Immunotherapy

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