Towards personalised medicine for cancer

From initial therapy to follow-up

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Chapter 24: General discussion

In 1971, a “war on cancer” was launched by the United States Congress and President Richard Nixon. This “war” led to considerable international commitments in cancer research and drug development, which ultimately catalysed numerous advances in our understanding of cancer biology and its treatment. However, 45 years after this war on cancer was launched, we are nowhere near reaching its ultimate goal – finding a cure – for the vast majority of cancer types. It has become increasingly clear that the war on cancer was based on a gross underestimation of the versatility, complexity, and resilience of the group of diseases that we call cancer. If anything, the most important result of the research efforts that were sparked by Nixon’s war on cancer is that we now have begun to understand how difficult it is to fully understand cancer. If we ever hope to cure a large proportion of patients suffering from cancer, we have to comprehend the complex interpatient and intrapatient heterogeneity that drives the need for individualised anti-cancer therapy at the level of the individual patient as well as the subclonal level in a neoplasm.

Since a few years, it is becoming clear that we should perhaps not classify cancer subtypes based on anatomy (e.g. brain cancer, leukaemia, and bile duct cancer) but instead classify cancer subtypes based on their molecular drivers (i.e. \textit{IDH1/2}-mutated or \textit{IDH1/2} wild-type cancer of glial cells, myeloid cells and cholangiocytes). This awareness was fuelled by large-scale, pan-cancer analyses of data derived from The Cancer Genome Atlas and showed that, for example, there is more molecular similarity between \textit{IDH1/2}-mutated glioblastoma and \textit{IDH1/2}-mutated leukaemia than between \textit{IDH1/2}-mutated glioblastoma and \textit{IDH1/2} wild-type glioblastoma. The biology of cancer consists of the sum of its parts, i.e. the molecular composition of the subclones of a neoplasm that ultimately results in symptoms at the clinical level. Therefore, the ideal treatment of cancer is targeted at molecular alterations that are shared between all subclones and thus arise very early in oncogenesis, such as \textit{IDH1/2} mutations that occur very early in the formation of glioma, chondrosarcoma, intrahepatic cholangiocarcinoma, and acute myeloid leukaemia (AML) (although in that case the data are conflicting). Therefore, because \textit{IDH1/2} mutations are early mutations, they seem interesting targets for molecular therapy for patients with \textit{IDH1/2}-mutated cancer. However, the early occurrence of \textit{IDH1/2} mutations in cancer may also present challenges for the treatment of late-stage disease with pharmacological inhibition of mutant \textit{IDH1/2}. With increasing mutational burden, the dependence of late-stage malignant tumours on mutant \textit{IDH1/2} most likely decreases and this diminishes the therapeutic index of \textit{IDH1/2}-mutant inhibitors. However, downstream effects of \textit{IDH1/2} mutations, such as the metabolic rewiring and the resulting energetic and metabolic stress, likely persist in late-stage \textit{IDH1/2}-mutated cancer. Therefore, we have hypothesised that this metabolic vulnerability of \textit{IDH1/2}-mutated cancer provides an excellent target for therapy. Treatment of \textit{IDH1/2}-mutated cancers with metabolically active agents such as metformin and chloroquine may be an interesting opportunity to repurpose these drugs that are already approved for other indications and it is attractive to investigate the effects of metformin and chloroquine in early-phase clinical trials with patients with \textit{IDH1/2}-mutated cancer. However, metformin and chloroquine are considered to be “dirty drugs” that target a plethora of cellular processes, which also increases the possibility of off-target effects and toxicity. At the end of the day, \textit{IDH1/2} “mutabolism” is ideally targeted with selective, small-molecule inhibitors of metabolic processes that are essential for \textit{IDH1/2}-mutated cancer cells but not \textit{IDH1/2} wild-type healthy cells.

Another downstream effect of \textit{IDH1/2} mutations that holds therapeutic potential is in the domain of exploiting reduced DNA damage responses. We have shown that \textit{IDH1/2} mutations make cancer cells relatively amenable to conventional cytotoxic agents (e.g. ionizing radiation, cisplatin, and daunorubicin), but also to targeted anti-cancer therapeutics, such as PARP inhibitors. Using our increased understanding of the biology of \textit{IDH1/2}-mutated cancers, we may be able to conceive...
combinatory regimens of lower doses of these classes of drugs that combine optimal therapeutic efficacy with minimal clinical toxicity.

The increased sensitivity of \textit{IDH1/2}-mutated cells against cytotoxic therapies is also suggested by data from our genomic sequencing effort of therapy-related myeloid neoplasms (t-MN) and therapy-unrelated myeloid neoplasms, where \textit{IDH1/2} mutations were more frequently observed in the latter than in the former. The relative scarcity of \textit{IDH1/2}-mutated t-MN suggests that any pre-existing \textit{IDH1/2}-mutated clones of haematopoietic stem and progenitor cells (HSPC) may have been wiped out by the preceding cytotoxic therapy that contributed to the propagation of the t-MN. Besides an interesting insight in the biology of \textit{IDH1/2}-mutated cells, this observation also supports the "mutation induction hypothesis" that states that t-MN is not exclusively caused by mutations induced by the preceding cytotoxic therapy, but that there may also be a role for a therapy-induced selective pressure on pre-existing mutant HSPC clones. Convincing evidence in support of this "clonal selection hypothesis" has already been presented by high-resolution sequencing of HSPC clones in blood samples of patients that were taken before starting a cytotoxic therapy for a first cancer. Patients that, often years later, developed a t-MN often had a \textit{TP53} mutant or haploinsufficient HSPC subclone in their HSPC compartment, whereas patients that did not develop t-MN had no such pre-existing mutant clones. Cytotoxic therapy may exert a selection of these \textit{TP53}-damaged subclones and it can be hypothesised that cytotoxic therapy can exert a selective pressure against pre-existing \textit{IDH1/2}-mutated subclones because of the relative sensitivity of these clones for cytotoxic agents.

Further evidence of this "clonal selection hypothesis" in t-MN development can be found in our studies on the increased risks for AML and myelodysplastic syndrome (MDS) after therapy with radioactive iodine (RAI) for well-differentiated thyroid cancer. RAI can be considered to be a circulating radiation emitter, but RAI doses are often low and may not achieve the threshold needed for mutagenicity in the HSPC compartment of the bone marrow. However, the RAI doses used in the treatment of well-differentiated thyroid cancer may be sufficient to exert a selection for pre-existing, mutant, pre-malignant clones, resulting in increased AML and MDS risks. Nonetheless, the relative risks for AML and MDS that we observed after RAI treatment were relatively low (below ten) as compared to an applicable background population. In comparison, the relative risks for AML development that we observed in a contemporary cohort of women with breast cancer that were treated with more intensive combination regimens of chemotherapy and radiotherapy were considerably higher (approximately twenty). This suggests that clonal selection cannot explain the entire issue of t-MN development. It seems plausible that the "clonal selection hypothesis" and the "mutation induction hypothesis" coexist, rather than that they are mutually exclusive. Combined chemotherapy and radiotherapy may result in both a selection for pre-existing mutant HSPC clones as well as the induction of additional mutations in them, which leads to high relative risks for t-MN development. The relatively low-intensity RAI treatment, as is applied for patients with well-differentiated thyroid cancer, may result in only a selective pressure for pre-existing mutant HSPC clones but not the introduction of novel mutations. Therefore, this could be the explanation why RAI treatment results in relatively lower, but still substantial, risks for t-MN development. Nonetheless, there is little or no clinical benefit of RAI treatment in most patients with well-differentiated thyroid cancer with low-risk or intermediate-risk disease features, and RAI treatment should be withheld from these cases. Every additional case of t-MN after the unnecessary administration of RAI is one too many and should be, when possible, avoided.

In line with this, a substantial amount of ongoing preclinical and clinical research is devoted to the question which cancer patients can be treated with less intensive treatment regimens so that toxicity and the occurrence of long-term adverse effects can be limited while the clinical outcomes that these less intensive treatment regimens confer do not become inferior to conventional high-intensity treatment regimens. Various chapters in this dissertation discuss severe long-term adverse effects of cytotoxic therapies such as the development of glioma after cytotoxic therapy at childhood age or
adolescent age or the incidence of heart disease-related mortality after exposure of the heart to ionising radiation in the context of radiotherapy for oesophageal cancer. We have shown that the occurrence of these long-term adverse effects is already decreasing. Major drivers behind this decrease are probably the use of less toxic chemotherapeutic agents, e.g. because alternatives for highly toxic drugs such as anthracyclines and classical alkylating agents have been developed, and technological improvements of radiotherapy have been implemented in the clinic so that ionising radiation can be delivered to the tumour with greater precision. However, increased risks of severe long-term adverse effects are still present. In contemporary cohorts where such risks currently do not reach the threshold of statistical and clinical significance, it is reasonable to doubt whether these increased risks are really abolished by the contemporary less-toxic treatment regimens, or simply more delayed. If the latter explanation would be true, this would be worrisome. Hypotheses that test this assumption deserve ongoing scrutiny as the epidemiological data matures.

In summary, considerable advances in our understanding of the biology of cancer and in the treatment of cancer have been acquired in the past decades. The awareness that every cancer is unique has spurred the philosophy that the ideal treatment of every cancer should also be unique. While this individualised type of anti-cancer therapy has not yet lived up to its promises – bringing significantly more cures to cancer patients – it cannot be denied that it is driving therapeutic advances that are already resulting in improved disease control with less toxicity. It is disputable whether or not the asymptote of finding a cure for all types of cancer will ever be reached, but in the future, an individualised war on cancer may get us eventually within the confidence interval of that utopia.