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The Future of Melanoma Therapy is the Combination Approach

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From a historical point of view, treatment of neoplastic disease can be considered one of the clearest example of the importance of combination strategies. In fact, a combination of surgery, radiotherapy and chemotherapy, is the best approach for the treatment of certain cancers such as breast cancer, ovarian and head and neck cancer.

However, not only cancer may benefit from combination therapy. Tubercolosis is a classical example of this concept [1]. After the discovery of Streptomycin in 1944, a new era for the treatment of tubercolosis dawned with further detection of Isoniazid, the first oral mycobactericidal drug in 1952 and Rifamycins in 1957. Sanatoria closed and truly effective public health measures became possible. Treatment was also increasingly expanded to include those with latent tuberculous infections. Furthermore, the introduction of Rifampicin in 1970 revolutionized the treatment of tuberculosis as, with its use in the context of combination strategies, the therapy of this infectious disease changed. In fact, use of antituberculosis drugs in monotherapy, including those of first choice, is strictly proscribed, since it might be easy to select spontaneously resistant germs. For this reason, drug regimens include associations of 3 or more drugs, variously alternated in relation to the clinical and developmental stages of tuberculosis (Table 1). Another aim of using drugs in combination was to eliminate bacterial subpopulations in various stages of metabolic activity and at different locations.

In the era of targeted therapy and development of novel therapies, the most important example in the context of combination therapies is Human Immunodeficiency Virus Syndrome (HIV). In fact, the discovery of several classes of drugs that act at different levels of the HIV virus, has caused a dramatic change in the prognosis of these patients. With the Highly Active Anti Retroviral Therapy (HAART), the famous drug cocktail, the definition of this disease has changed from incurable to a chronic illness [2].

Drug used in Standard regimens for new TB patients	
(presumed, or known, to have drug-susceptible TB)	
Intensive phase treatment	**Continuation phase**
2 months	**4 months**
HRZE regimen	*HR regimen*
Isoniazid (H)	*Isoniazid (H)*
Rifampicin (R)	*Rifampicin (R)*
Pyrazinamide (Z)	
Ethambutol (E)	
streptomycin	
In tuberculous meningitis, ethambutol should be replaced by streptomycin.	
(in settings where the level of isoniazid resistance among new TB cases	
is high and isoniazid susceptibility testing is not done	
(or results are not available) before the continuation phase begins	
Intensive phase treatment	**Continuation phase**
2 months	**4 months**
HRZE regimen	*HRE regimen*
isoniazid	*isoniazid*
rifampicin	*rifampicin*
pyrazinamide	*ethambutol*
Ethambutol	

Table 1: Adapted from Treatment of tubercolosis: guidelines for national programmes. Fourth edition. World Health Organization. http://www.who.int/tb/features_archive/new_treatment_guidelines_may2010/en/index.html

From a historical point of view, the introduction of target agents trastuzumab in 1998 and imatinib in 2001 led to the era of targeted therapy in oncology. More than 10 years have since passed and more and more innovative treatment details have been reached. Ipilimumab is a further example of what has been said. The use of a target agent that, through an indirect action on the immune system, shows antineoplastic activity against cancers such as melanoma, prostate cancer and NSCLC, was not even imaginable a few years ago. In March of this year FDA approved the ipilimumab in the treatment of advanced melanoma and in June it was published the positive results of the combination dacarbazine + ipilimumab as first line treatment of advanced melanoma [3]. This could be considered the start of the combination approach in melanoma therapy.

The failure of first approaches to vaccine therapy [4] and the controversial role of interferon in some cancers (melanoma and renal cancer cell) have made the world of oncology skeptical about immunotherapy. The year 2010, from this point of view, has been a fantastic year. In fact, this was the year in which the first vaccine therapy showed effectiveness in oncology: Sepuleucel-T in the treatment of prostate cancer (the first anti-cancer vaccine which received FDA approval) [5]. Furthermore, the first phase III study demonstrated a survival advantage in malignant melanoma through the use of ipilimumab, even if second line [6]. Moreover, year 2010 brought news not only in the field of immunotherapy. Vemurafinib (well known as PLX4032), or the specific inhibitor of BRAF V600E in the mutated form, was another important achievement in the field of oncology [7]. In fact, considering that 50% of patients with melanoma has V600E mutation in BRAF protein, resulting in a proliferation signal always active, having found an agent that could inhibit the activity of this kinase could be the beginning of a new era for the treatment of melanoma.

For several years, sorafenib, a multi-kinase inhibitor, kindled hopes of a breakthrough in the treatment of melanoma. The phase II study published by Flaherty [8] showed a median progression free survival (PFS) of 8.8 months in combination with carboplatin and paclitaxel compared with 1.7 months for historical controls [9]. Unfortunately, subsequent phase II-III studies have not confirmed the initial data of the study of Flaherty [10-12]. However, considering the positive

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Drug Classes active in melanoma			
Kinase inhibitors	**Immunomodulating antibodies**	**Chemothepateutics Agents**	**Vaccination**
iBRAF	ipilimumab	DTIC	MAGE A3
iMEK	Anti-PD1	TMZ	PRAME
ic-Kit	Anti-CD137	FTM	NY-ISO1
iPI3K	Anti-CD40	CDDP	
iAKT	OX40	Paclitaxel	IL2 + gp100
imTOR	Anti TGF b	NAB-paclitaxel	
	L19IL2		
PARP inhibitors	**Immunomodulating small molecule**	**Anti-angiogenic Agents**	**Plasmid/ Oncolytic Virus**
ABT-888	1 MT		Allovectin-B7
			Onco-Vex
GSI	**HDAC**	**Pro-apoptotic Drugs**	**Adoptive Cell therapies**

Table 2:

Current HAART Drugs		
NRTI	**PI**	**Integrase Inhibitor (II)**
Abacavir (ABC)	Atazanavir (ATV)	Raltegravir (RAL)
Didanosine (ddI)	Darunavir (DRV)	
Emtricitabine (FTC)	Fosamprenavir (FPV)	**Fusion Inhibitor**
Lamivudine (3TC)	Indinavir (IDV)	Enfuvirtide (ENF, T-20)
Stavudine (d4T)	Lopinavir (LPV)	
Tenofovir (TDF)	Nelfinavir (NFV)	**CCR5 Antagonist**
Zidovudine (AZT, ZDV)	Ritonavir (RTV)	Maraviroc (MVC)
	Saquinavir (SQV)	
NNRTI	Tipranavir (TPV)	
Delavirdine (DLV)		
Efavirenz (EFV)		
Etravirine (ETR)		
Nevirapine (NVP)		
NRTI = Nucleoside Reverse Transcriptase Inhibitor		
NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor		
PI = Protease Inhibitor		

Table 3A: Adapted from "AIDS Education and Training Centers - National Resource Center. Comprehensive Guideline Summary. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents. January 2011. http://www.aidsetc.org"

Initial Treatment: Preferred	
NNRTI based	EFV/TDF/FTC1,2
PI based	ATV/r + TDF/FTC[2]
	DRV/r (QD) + TDF/FTC[2]
II based	RAL + TDF/FTC[2]
Pregnant women	LPV/r (BID) + ZDV/3TC[2]
1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.	
2. 3TC can be used in place of FTC and vice versa	

Table 3B:

results of the BRIM3 study published this year [13], the original idea of targeting BRAF was not wrong. It was wrong to a servant who, despite the in vitro results, did not look similar in vivo. Verumafinib showed, in ^{V600E}BRAF mutated population, a relative reduction of 63% in the risk of death and of 74% in the risk of disease progression [13]. This episode should teach us that sometimes, despite a good original idea, not always what is believed to be an active drug on the basis of in vitro experiments is an effective form of therapy in vivo and thus the original idea should be better refined.

A discussion about combination strategies could start from the example of melanoma. In fact, after 30 years of disappointments and almost non-existent care, this disease has been going through a plethora of treatment possibilities (Table 2). Ipilimumab and vemurafinib represent the starting point for more effective melanoma treatment. Considering the currently available drugs with activity against melanoma, it would be desirable to somehow repeat what happened in the treatment of HIV with HAART. In fact, we should learn from the HAART, a combination of three or four different antiretroviral drugs (reverse transcriptase and protease inhibitors) often referred to as "drug cocktail", used to treat patients with HIV infection (see Table 3A-B). HAART inhibits HIV replication, keeps the HIV offspring low and reduces the chances of HIV mutation because each drug attacks HIV through a different mechanism. A similar approach for the therapy of melanoma using drugs with different mechanisms of action, for example on MAPK pathway, P3I3-mTOR pathway, apoptosis pathway and immunological monoclonal antibodies, could be considered. A multi-target therapy could combine novel agents with standard therapy (Dacarbazine, Temozolomide, other chemotherapic agents). Sequential administration of different agents may inhibit cancer cell growth at different check points, while other agents may inhibit neo-angiogenesis, survival of malignant cells or metastatization, converting melanoma into a chronic disease [14,15].

Possibly, it would be better to interfere simultaneously on various pathways involved in melanoma progression. Comparing the number of pathways to parallel electric circuits, it is unlikely that single on off switch will be sufficient. It is likely that several triggers may constitutively activate different and complex processes which could then give different characteristics to the malignant cell [14,15].

Melanoma can become a model in cancer therapy. Today we have these two drugs (ipilimumab and vemurafinib) that have different characteristics and effectiveness, one (vemurafinib) that acts immediately, with a median latency of 6-7 months before developing resistance, the other (ipilimumab) with a slower (months) but more lasting (years) action. The first step is, of course, the combination of these two agents, but the real challenge is to bypass the mechanisms of resistance and improve the effectiveness of ipilimumab. In addition, we need to identify combined approaches for those patients (representing another 50%) who do not have the BRAF mutation. New molecular studies will certainly give us some important news for this subset of patients.

The toxicity will surely be a high price to pay. In fact, it is known that the combination of different compounds can amplify the side effects of every single drugs. The HAART is an example of toxicity from the combination of several drugs [16]. However, this could be the price for turning melanoma from an incurable disease into a manageable disease.

In the past year, Dr Donald Morton from the John Wayne Cancer Institute of Santa Monica (USA) had sentenced that surgery was the best efficacy approach to melanoma even in advanced disease. His watchword was "Surgery, surgery, surgery". I think that it's started a new era with a new watchword: "Combine, combine, combine".

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