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Approach to a Guideline for Epigenetic Therapy in the High Risk Cancer Setting

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Editorial

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Abbreviations: DNMTI: DNA Methyl Transferase Inhibitors; HDACI: Histone Deacetylase Inhibitors; CTCL: Cutaneous T-Cell Lymphoma; PTCL: Peripheral T-Cell Lymphoma; SCT: Stem Cell Transplant; AML: Acute Myeloid Leukemia; CMML: Chronic Myelomonocyticleukaemia; NHL: Non-Hodgkin Lymphoma; HL: Hodgkin's Lymphoma; NSCLC: Non-Small Cell Lung Cancer; TET: ten-eleven translocation

Introduction

The term 'epigenetics' had been originally described by Waddington in 1939; and after substantial changes in the definition, it has been finally defined as "the study of "heritable changes in gene expression, capable of altering cellular phenotype and function independent of alterations in DNA sequence", which has now been a focus of intensive research as a promising ambition for the management of malignant disorders [1]. There has been a large number of clinical trials investigating effects of therapeutic agents targeting epigenome of cancer patients, though the majority of them are early phase studies and there is scarcity of powerful data coming from randomized clinical trials with large patient populations in this setting. However, despite their less strong data coming from early phase studies, when the study is about patients of hard to manage categories, including older patients or those who have already shown refraction to the conventional therapy or relapsed after the primary treatment course, any promising result even if coming from less robust methodologies could be considered valuable or even inevitable. To address this issue, this editorial aims to provide an overview on the promising evidence on the positive effects of epigenetic treatments in the higher risk cancer patients, as defined above, and also to offer an abstracted approach to a guideline for targeted epigenetic therapy in this population, based on the current available data in the literature.

Monotherapy with DNA Methyltransferase Inhibitors (DNMTi)

Although cancer tissues commonly experience global hypomethylation of their genome, focal hypermethylations occurring in the promoter CpG islands leads to silencing of several critical TSGs. This factor alongside the silencing of oncogenes through methylation of their genes bodies (and not promoters) as well as, silencing the second allele of a TSG gene in a Knudson's two-hit models makes DNMTi agents valuable in the context of cancer therapy [2]. DNMTi monotherapy has usually been investigated in the hematological malignancies, but it has been of very limited –if any- use in the non-hematological cancers.FDA has already approved azacitidine and decitabine for using in a number of hematological malignancies; and while a systematic review suggests more promising therapeutic efficacy for azacitidine versus decitabine, there is on the other hand evidence suggestive of decitabine efficacy in azacitidine-resistant MDS [3-4]. The most rigorous evidence about efficacy of DNMTi monotherapy in cancer patients comes from two pivotal clinical trials, AZA-MDS-001 and AZA-AML-001, whose data served the main evidence for the approval of these drugs for use in hematological diseases. Some of the most important clinical studies with positive responses reported for DNMTi therapy in cancer high-risk populations have been presented in Table 1.

Monotherapy with Histone deacetylase inhibitors (HDACI)

Histone dacetylases are a group of enzymes that eliminate acetyl groups from histones and can regulate expression of tumor suppressor genes, and HDACi agents inhibit their activity. To date, three HDACi agents have been approved for cancer therapy by the FDA that includes Vorinostat (SAHA, Zolina), for use in patients with cutaneous T-Cell Lymphoma (CTCL), a rare type of

non-Hodgkin's lymphoma of the skin; romidepsin (Istodax, FK228, FR901228, depsipeptide), for the treatment of T-cell lymphoma, and belinostat (Beleodaq, PXD-101), for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) [5].Although HDACi monotherapy in hematological and lymphoproliferative malignancies had been associated with promising results, the outcome of clinical trials in patients with solid tumors, except for individual reports with some modest effects, had been disappointing. For example, as a study with a most encouraging result, a phase II trial of patients with recurrent glioblastomamultiforme, vorinostat mono therapy resulted in progression free survival in only 9 out of 52 patients [6].Two invaluable review articles have recently published studying effects of DNMTi agents on solid tumors which can be used for more information [7-8]. Some of the most promising results coming from clinical trials on the impact of HDACi therapy in the hard to manage cancer patients is included in Table1.

Clinical Evidence for DNMTi Plus HDACi Therapy Efficacy

Although neither DNMTi nor HDACi agents represented any encouraging outcomes in the management of solid tumors when administered as single agent, dual therapy of solid tumors employing agents from these two groups had satisfactory results. On the other hand, results of this combination therapy in hematological cancers were more disappointing [9]. An explanation for this observation had been provided by Prebet et al., which speculated on the cell-cycle inhibition potency of some HDAC inhibitors and its potential inhibitory impact on the DNMTi incorporation into the DNA, when administered concomitantly, leading to poorer outcomes than monotherapy with DNMTi [10]. Some of the most successful concomitant employment of DNMTi and HDACi in the high-risk cancer patients is represented in Table 1.

Combination of epigenetic agents with chemotherapy

Chemotherapy is the backbone of patient management in most malignant disorders; nevertheless, its application is not always pertinent due to either the magnitude of its efficacy or associated side effects, in different cancer subpopulations. The epigenetic agents, despite their limitations of use, including own side effects as well as efficacy power, have been shown to be safe and efficacious in specific subpopulations of cancer patients, when administered concomitant or sometimes before the conventional chemotherapy. Selected studies representing some of the most promising evidence from the literature in this regard could be found in Table 1.

Cytogenetic and Epigenetic Predictors

Considering the principle topic of the current study, maybe the most important factor that may predict response to therapy in cancer patients is epigenomic status of their malignant lesions. In a comprehensive systematic review on microRNAs and their association to chemotherapy efficacy in gastric cancer cell lines, this author found an interesting similarity in the target genes of microRNAs that most greatly affect the same chemotherapy agent, suggesting that dysregulation of particular genes may predict resistance or sensitivity to specific chemotherapy agents [11]. So, it would not be surprising if particular cytogenetic or epigenetic signature of a cancer lesion well predict efficacy of a specific epigenetic-and/or chemo-therapy agent in those patients. For example, azacitidine is suggested to improve response rates in AML patients with ten-eleven translocation 2 (TET2) mutations compared with its wild type, while patients withTP53 mutations represent poorer overall survival in response to azacitidine therapy than those without the mutation [reviewed by ref 12]. Based on this fact, some prognostic scoring systems have been developed to predict cancer therapy results. A review article by Treppendahl *et al.* has listed molecular predictors for response to epigenetic therapy in cancer patients, and those fit this paper can be found in Table 1 [13].

Conclusion

Approach to a Guideline development

In order to develop a guideline for targeted use of epigenetic therapy in cancer patients, we would need robust evidence coming from studies employing rigorous methodology and enough sample size; however studies investigating efficacy of epigenetic therapy in cancer patients mainly are of early phase and include limited number of patients. On the other hand, there are studies investigating this effect in patients of higher risk settings, for whom there are few or no therapeutic choices are available. In these cases, at least, promising, data coming from even less powerful methodologies might worth to try in the clinical practice, until more vigorous data gets into enters the literature. In Table 1, a list of epigenetic therapies which had been associated with clinical response to epigenetic treatment in high-risk cancer patients is provided. The main approach in this paper was to exclude studies with very limited number of participants unless those with the most important, powerful results, or most distinctive cancer subgroups. Studies with the highly robust methodologies have been mentioned in bold

font. Further A phase III studies in these cancer subpopulations empower us to prepare a more reliable guideline to manage these patients more steadily.

Cancer type	Subpopulation	n	Treatment	Limitation/power	Ref. (clinicaltrials.gov)
AML/MDS	**Elderly**	**488**	**Azacitidine [Approved by FDA, EMA]**	**Survival benefit/Phase III trial**	**NCT01074047**
	Elderly with high miR-29 level	53	decitabine	Clinical response	NCT00492401
	Elderly with poor/interm. cytogenetics	**485**	**Decitabine [Approved by FDA, EMA]**	**Phase III trial/clinical response/NSS survival benefit**	**NCT00260832**
	Elderly + multiple comorbidities	227	Azacitidine(vs. IC)	Less side effects/similar survival	doi: 10.1186/1756-8722-6-29
	Elderly	50	Azacitidine + pracinostat	Clinical response/Nd. RND	NCT01912274
	Elderly non-fit AML	204	Decitabine + (ATRA vs. VPA)	Survival benefit/randomized trial	NCT00867672
	Poor cytogenetics	**358**	**Azacitidine (vs. LDAC/CCR)**	**Phase III/Much better survival**	NCT00071799
	Relapsed/refractory	66	Mocetinostat + azacitidine	Phase II study; 2/3rd of patients achieved CR/nd. RND	NCT00324220
	Relapsed/refractory	36	Decitabine + ATRA	Good survival/nd. RND	doi: 10.1007/s00277-016-2681-3
	Relapsed/refractory/Response only in CMML subgroup	260	Azacitidine + lenalidomide	Clinical response/randomized trial	NCT01617226
Lymphoma	Relapsed/refractory NHL	35	Vorinostat	49% ORR, 20 mo PFS/nd RND	NCT00253630
	Relapsed/refractory HL	37	Resminostat	~50% clinical response/Nd. RND	NCT01037478
	Relapsed/refractory PTCL	74	**Romidepsin [Approved by FDA]**	~25% clinical response/nd. RND	NCT00091559
	Relapsed/refractory PTCL	47	Romidepsin	38% response rate/nd. RND	NCT00007345
	Relapsed/refractory HL after autologous SCT	129	Panobinostat	**Tumor reduction in 74%; 1 yr survival in 78%/nd. RND**	NCT00742027
	Progressive/relapsed peripheral T cell lymphoma	131	Romidepsin	~25% Clinical response	NCT00426764
	Relapsed/refractory lymphoma	29	Vorinostat + rituximab + ifosfamide + carboplatin + etoposide	~2/3rd of patients clinically responded/nd. RND	NCT00601718
Ovary	Platinum-resistant/refractory	30	Azacitidine + carboplatin	ORR:22%, median OS: 23 mo/nd. RND	doi: 10.1002/cncr.25701
	Platinum-resistant/refractory	28	Decitabine + carboplatin	Up to 70% response rate; PFS~10mo/nd. RND	NCT00477386 (conflicting results to doi: 10.1038/bjc.2014.116 with recurrent cancer patients)
	Relapsed or refractory	80	Belinostat + carboplatin + paclitaxel	43% clinical benefit/nd. RND	NCT00421889

	Stage III/IV	18	Vorinostat + paclitaxel + carboplatin	18/18(100%) PFS up to 24 months/nd. RND	NCT00976183
Cervix	**Stage IVB**	**143**	**VPA + hydralazine + cisplatin + topotecan**	**Survival benefit/Phase III randomized trial**	NCT00532818
	Relapsed and metastatic	25	Decitabine + cisplatin	~62% response rate/nd. RND	[14]
Breast	**ER+/ exemestane-resistant**	**600**	**Entinostat + exemestane**	**Survival benefit/Phase II/randomized trial**	NCT02115282
	Male/high stage	54	Vorinostat +paclitaxel + bevacizumab	~49% stable disease/nd. RND	NCT00368875
	Hormone-therapy resistant	43	Vorinostat + tamoxifen	6 mo stable dis. ~40%/nd. RND	NCT00365599
NSCLC	Progressive & metastatic with hypermethylation of > 2/4 genes*	10	Azacitidine + entinostat	Remission occurred/nd. RND	NCT01935947
	Stage IIIB/IV with E-cadherin (+)	**70**	**Erlotinib + entinostat**	**Randomized phase II trial/survival benefit**	NCT00750698
	Stage IIIB/IV	62	Vorinostat/placebo + (carboplatin+ paclitaxel)	34% vs. 12.5 response; NSS survival benefit/Phase II randomized trial	NCT00481078 (conflicting results with trials [NCT01413750 & NCT00473889)
Multiple myeloma	**Progressive/non-refractory**	**317**	**Bortezomib + vorinostat**	**Randomized phase III trial; significant survival benefit (7.6 vs. 6.8 mo)**	**NCT00773747**
	Relapsed	768	Panabinostat/placebo + Dexamethasone + Bortezomib	**Phase III randomized trial:** ORR:~61% vs. 55%; NSS	NCT01023308
	Relapsed &Bortezomib refractory	55	Panabinostat + Dexamethasone + Bortezomib	~52% response; ~34% ORR/nd. RND	NCT01083602
	Relapsed or refractory	40	Romidepsin + bortezomib + dexamethasone	25% response rate (durable response)/nd. RND	NCT00431990
Hepato-cellular carcinoma	Progressive & advanced &sorafenib refractory	57	Resminostat +/- sorafenib	Survival benefit/comparative phase I/II trial/ nd. RND	NCT00943449
Polycythemia vera	Unresponsive to TMD of HC	44	Givinostat + TMD of HC	Clinical response/nd. RND	DOI: 10.1111/bjh.12332
Colorectal	Irinotecan-resistant	108	Guadecitabine + irinotecan	~60% response rate/nd. RND	NCT01896856
Kidney cancer	Unresectable or metastatic	37	Vorinostat + Bevacizumab	~69% response rate/nd. RND	NCT00324870

*interm: intermediate; AML: acute myeloid leukemia; CMML: chronic myelomonocyticleukaemia; NHL: non-Hodgkin lymphoma; HL: Hodgkin's lymphoma; PTCL: Peripheral T cell lymphoma; SCT: Stem cell transplant; NSCLC: Non-small cell lung cancer; 4 genes include: APC, RASSF1A, CDH13, and CDKN2A; nd. RND: Needs randomized trials for confirmation

Table 1: Selected studies representing most efficient evidence on epigenetic therapies in high-risk cancer populations

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