Editorial

Tumor lysis syndrome caused by therapeutic monoclonal antibodies approved by FDA

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Editorial

In 1975, Monoclonal antibody (mAb) technique was created by Georges Köhler, César Milstein, and Niels Kaj Jerne by using mouse x mouse hybridoma, they shared the Nobel Prize in Physiology or Medicine in 1984 for the discovery. 8 years later, in 1992 FDA approved first therapeutic mAb Muromonab-CD3 (trade name Orthoclone OKT3) to reduce acute rejection in patients with organ transplants, since then, as of May 31, 2017, FDA has approved 70 therapeutic mAbs.[1–3] Among them 28 were approved for treatment of cancers (Table 1).[4–31] These therapeutic mAb targets at components expressed on cancer cell, possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC), antibody-dependent cell mediated cytotoxicity (ADCC), induced apoptosis, cancer cell growth inhibition, direct cytoxicities, and conjugates indirect effect resulting cancer cell death (radiation or internalized derives). Unfortunately, so far there is no tumor specific antigen (TSA) available for target, those antigens chosen as target, they also expressed at normal cells, which inevitably causes various adverse reactions, in this article, tumor lysis syndrome (TLS) is briefly reviewed.

TLS may be a consequence of liquid tumor treatment with therapeutic mAbs approved by FDA (Table 2), which is not seen in the labeling of therapeutic mAbs for solid tumor (Table 3). Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12-24 hours after the first infusion of the therapeutic mAbs. Interestingly among those therapeutic mABs for liquid tumors, even targeting same antigen CD20, it may not cause TLS (Table 2). It is believed patients with high tumor burden, high circulating lymphocyte count (> 25 x 109 /L) or renal impairment are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol or rasburicase) and hydration prior to the infusion of the therapeutic mAb. Physicians should also consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white blood count to < 30,000/μL prior to administration of the therapeutic mAb. During the initial days of treatment, monitor the laboratory parameters of patients considered at risk for TLS. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Table 1 Monoclonal Antibodies for Cancer Therapy Approved By FDA.

Drug name	Approval date	Company	Active integedients	Target	Indication
Rituxan	11/26/1997	IDEC	Rituximab	CD20	B-NHL
Herceptin	9/25/1998	Genetech	Trastuzumab	EGF	Breast Ca
Mylotarg	5/17/2000	Wyeth	Gemtuzumab Ozogamicin	CD33	AML
Campath	2/7/2001	Genzyme	Alemtuzumab	CD52	B-CLL
Zevalin	2/19/2002	Spectrum	Ibritumomab Tiuxetan	CD20	B-NHL
Erbitux	2/12/2004	Imclone	Cetuximab	VEGFR	MCC
Avastin	2/26/2004	Genetech	Bevacizumab	VEGF	Colon Ca
Vectibix	9/27/2006	Amgen	Panitumumab	EGFR	Colorectal Ca
Arzera	10/26/2009	Glaxo	Ofatumumab	CD20	B-CLL
Yervoy	3/25/2011	BMS	Ipilimumab	CTLA-4	Melanoma
Adcetris	8/19/2011	Seattle Sci	Brentuximab Vedotin	CD30	HL
Perjeta	6/8/2012	Genetech	Pertuzumab	HER2	Breast Ca
Kadcyla	2/22/2013	Genetech	Ado-Trastuzumab Emtansine	HER2	Breast Ca
Gazyva	11/1/2013	Genetech	Obinutuzumab	CD20	B-CLL
Cyramza	4/21/2014	Eli Eilly	Ramucirumab	VEGFR2	Gastric Ca
Ketruda	9/4/2014	MSD	Pembrolizumab	PD-1	Melanoma
Bexxar	12/3/2014	Amgen	Tositumomab; Iodine I 131 Tositumomab	CD19+CD3	ALL
Opdivo	12/22/2014	BMS	Nivolumab	PD-1	Melanoma
Unituxin	3/10/2015	United Terap	Dinutuximab	GD2	Neuroblastoma

Table Continued...

Drug name	Approval date	Company	Active integedients	Target	Indication
Darzalex	11/16/2015	Janssen	Daratumumab	CD38	MM
Portrazza	11/24/2015	Eli Eilly	Necitumumab	EGFR	Lung cancer
Empliciti	11/30/2015	BMS	Elotuzumab	SLAMF7	MM
Tecentiq	5/18/2016	Genetech	Atezolizumab	PD-L1	Urothelial Ca
Tecentriq	10/18/2016	Genetech	Atezolizumab	PD-L1	Metastatic NSCLC
Lartruvo	10/19/2016	Eli Eilly	Olaratumab	PDGFR-α	soft tissue sarcoma
Bavencio	3/23/2017	EMD serono	Avelumab	PD-L1	Metastatic Merkel Cell Ca
Imfinzi	5/1/2017	Astrazeneca UK	Durvalumab	PD-L1	Metastatic Urothelial Ca
Bavencio	5/9/2017	EMD serono	Avelumab	PD-L1	Metastatic Urothelial Ca

CD, cluster of differentiation; EGF, epidermal growth factor;VEGFR, vascular endothelial growth factor receptor;VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; CTLA-4, cytotoxic t-lymphocyte-associated protein 4; HER2, human epidermal growth factor receptor 2; PD-1, programmed cell death protein 1; GD2, glycolipid disialoganglioside; SLAMF7, signaling lymphocytic activation molecule family member 7; PD-L1, programmed death-ligand 1; B-NHL, B-cell non-hodgkin's lymphoma; AML, acute myeloid leukemia; B-CLL, B-cell chronic lymphocytic leukemia; MCC, metastatic colorectal carcinoma; HL, hodgkin's lymphoma; ALL, acute lymphocytic leukemia; MM, multiple myeloma; PDGFR-α, platelet-derived growth factor receptor alpha; MCC, merkel cell carcinoma

Table 2 Therapeutic Monoclonal Antibodies for Liquid Tumor Therapy Approved By FDA

Drug name	Approval date	Company	Active integedients	Target	Indication	TLS
Rituxan	11/26/1997	IDEC	Rituximab*	CD20	B-NHL	Yes
*Mylotarg	5/17/2000	Wyeth	Gemtuzumab Ozogamicin	CD33	AML	Yes
Campath	2/7/2001	Genzyme	Alemtuzumab	CD52	B-CLL	No
Zevalin**	2/19/2002	Spectrum	Ibritumomab Tiuxetan	CD20	B-NHL	No
Arzerra*	10/26/2009	Glaxo	Ofatumumab	CD20	B-CLL	Yes
Adcetris*	8/19/2011	Seattle Sci	Brentuximab Vedotin	CD30	HL	Yes
Gazyva*	11/1/2013	Genetech	Obinutuzumab	CD20	B-CLL	Yes
Darzalex	11/16/2015	Janssen	Daratumumab	CD38	MM	No
Empliciti	11/30/2015	BMS	Elotuzumab	SLAMF7	MM	No
Bexxar	12/3/2014	Amgen	Tositumomab; Iodine I 131 Tositumomab	CD19+CD3	ALL	N/A

Table 3 Therapeutic Monoclonal Antibodies for Solid Tumor Therapy Approved By FDA

Drug name	Approval date	Company	Active integedients	Target	Indication	TLS
Herceptin	9/25/1998	Genetech	Trastuzumab**	EGF	Breast Ca	No
Erbitux	2/12/2004	Imclone	Cetuximab	VEGFR	MCC	No
Avastin**	2/26/2004	Genetech	Bevacizumab	VEGF	Colon Ca	No
Vectibix	9/27/2006	Amgen	Panitumumab	EGFR	Colorectal Ca	No
Yervoy**	3/25/2011	BMS	Ipilimumab	CTLA-4	Melanoma	No
Perjeta**	6/8/2012	Genetech	Pertuzumab	HER2	Breast Ca	No
Kadcyla**	2/22/2013	Genetech	Ado-Trastuzumab Emtansine	HER2	Breast Ca	No
Cyramza**	4/21/2014	Eli Eilly	Ramucirumab	VEGFR2	Gastric Ca	No
Keytruda**	9/4/2014	MSD	Pembrolizumab	PD-1	Melanoma	No
Opdivo**	12/22/2014	BMS	Nivolumab	PD-1	Melanoma	No
Unituxin**	3/10/2015	United Terap	Dinutuximab	GD2	Neuroblastoma	No
Portrazza**	11/24/2015	Eli Eilly	Necitumumab	EGFR	Lung cancer	No

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None.

Conflicts of interest

The authors declare no conflicts of interest.

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