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The adverse events profile of anti-IGF-1R monoclonal antibodies in cancer therapy

Honghai Ma,[1] Tiehong Zhang,[2] Hongchang Shen,[2] Hongxin Cao[2] & Jiajun Du[2]

[1]Department of Thoracic Surgery, Provincial Hospital Affiliated to Shandong University, Shandong University, Jinan, China and [2]Institute of Oncology, Provincial Hospital Affiliated to Shandong University, Shandong University, Jinan, China

Correspondence
Professor Jiajun Du, Department of Thoracic Surgery, Provincial Hospital Affiliated to Shandong University, Shandong University, 324 Jingwu Road, Jinan, 250021 China.
Tel: +86 531 8518 7837
Fax: +86 531 8518 7837
E-mail: dujiajun@sdu.edu.cn

Ma, HH and Zhang, TH contribute equally to this work.

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AIM(S)

Insulin-like growth factor-1 receptor (IGF-1R) targeted therapies have become one of the intriguing areas in anticancer drug development during the last decade. As one of these therapies, anti-IGF-1R monoclonal antibodies (mAbs) are also advancing further in development. Our purpose was to conduct a systematic review of the adverse events (AEs) caused by anti-IGF-1R monoclonal antibodies in cancer therapy.

METHODS

We searched the term'IGF-1R monoclonal antibody' in the Pubmed database and found 389 related articles. After elaborate selection, 15 clinical studies that satisfied our criteria were then adopted for further analysis. We extracted all the useful information about the AEs of mAbs from the enrolled studies. Every kind of reported AE as well as corresponding incidences were summed up and calculated. We compared AE incidence differences in two age groups, and analyzed toxicities of mAbs used as a single agent or combined with chemotherapies. Finally, the differences of AE profiles between individual mAbs were also valued.

RESULTS

AEs were more severe in the lower age group and 13 of 19 AE incidences in the single-agent group were significantly lower than in the combination group ($P < 0.05$). R1507 seemed to show a worse AE profile than cixutumumab and figitumumab.

CONCLUSIONS

When anti-IGF-1R mAbs are used for cancer therapy, it is essential to choose the proper drug and combined chemotherapies to reduce AE occurrences. Also, administration of these mAbs to younger patients should be more carefully supervised. Furthermore, some more frequently observed AEs for specific mAb should be paid adequate attention.

Introduction

Insulin-like growth factor-1 receptor (IGF-1R) targeted therapy has become one of the most investigated areas in anticancer drug development during the last decade [1]. Experimental exploration and studies of clinical tumour biopsy specimens suggest that cancer progression is frequently associated with increased expression of the IGF-1R. There are a broad range of tumour types such as breast, colon, sarcoma, lung, prostate, thyroid and myeloma that aberrantly express IGF-1R. Therefore the strategy of blocking IGF-1R activity is of possibly great use in the treatment of various cancers [2]. Monoclonal antibodies (mAbs) targeting IGF-1R are one of these strategies. Unfortunately, the result of phase III trial of carboplatin and paclitaxel with or without figitumumab was disappointing and patients who received figitumumab suffered from more severe adverse events (AEs) such as early fatal toxicities [3]. Besides, Roche decided to suspend the development of R1507 for

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business reasons [4]. Despite all these pitfalls, IGF-1R remains an attractive anticancer target and several ongoing trials are testing anti-IGF-1R mAbs or in combination with chemotherapy in patients with malignant tumours, such as pancreatic and ovarian cancer [5]. In the current environment of similar IGF-1R-targeted agents competing for similar patient populations, differences in the frequency and intensity of AEs may be an important determinant as to whether a mAb will win out, although AEs caused by these mAbs were generally reported to be tolerable in early clinical trials [2, 6]. We conducted this systematic review to assess the AEs described in former clinical studies and hoped to provide significant information for further research of these mAbs.

Methods

Search methods and study selection

We searched 'Pubmed' using the search term 'IGF-1R monoclonal antibody'. From 389 achieved articles published before April 20 2012, we selected the studies that met each of following criteria: 1) clinical studies were concerned with the use of any anti-IGF-1R mAbs for treatment of malignant tumours, 2) patients' demographics and baseline disease characteristics were clearly demonstrated, 3) most AEs occurred during a whole specific clinical study process were given in a clear fashion, and the baseline of AEs were 'AE with its incidence >5%' or 'AEs grade ≥2' (there were two exceptions, the baseline for studies 8 and 9 was ≥10%, but the two samples' sizes were small thus and this baseline was indeed acceptable), 4) AEs were graded using the same criteria: 'National Cancer Institute Common Terminology Criteria for Adverse Events' (version 3.0) and 5) AEs were counted in numbers of patients experiencing them, rather than the observed episodes of AEs.

Data extraction

Two independent investigators (Honghai Ma and Hongxin Cao) reviewed the publications and extracted the data. Every enrolled study was given a 'study number' and details are shown in Table 1. The following information was extracted from each article: 1) basic information from papers such as year of publication, journal name and authors' name, 2) characteristics of patients such as age, gender and tumour type, 3) information of study designation such as phase I/II and treatment protocol, 4) information on treatment such as treatment modality, dose of chemotherapy and 5) number of patients experiencing AEs during the whole clinical trial. Available information was extracted and recorded to a data collection form and entered into an electronic database.

Table 1

Characteristics of studies included in the analysis

Study number	Study	Number of patiens	Gender (male/female)	Median (range) age (years)	Tumour type	Study phase	Drugs	The baseline for including AEs
1	Kurzrock *et al.*, 2008 [14]	35	23/12	48.3 (18–74)	Advanced solid tumours	I	R1507	All
2	Tolcher *et al.*, 2009 [29]	53	38/15	54 (22–84)	Refractory solid tumours	I	Ganitumab	All
3	Naing *et al.*, 2011 [30]	42	19/23	53 (20–79)	Advanced cancer	I	CIX and Torisel	All
4	Molife *et al.*, 2010 [25]	46	40/6	59.4 (25–79)	Advanced solid tumours	Ib	CP and DOC	All figitumumab related
5	Karp *et al.*, 2009 [22]	42	24/18	60.5 (26–80)	Advanced cancer	Ib	CP and PAC and CB	>5% figitumumab related
6	Olmos *et al.*, 2010 [27]	29	21/8	30 (12–63)	Sarcoma and Ewing's sarcoma	I	CP	All
7	Atzori *et al.*, 2011 [31]	80	40/40	57 (19–81)	Advanced solid tumours	I	Dalotuzumab	All
8	Weickhardt *et al.*, 2012 [9]	18	8/10	65 (48–77)	Advanced NSCLC	I/II	CIX and erlotinib	≥10%, or ≥grade 3
9	Quek *et al.*, 2010 [32]	21	12/9	56 (25–77)	Advanced sarcomas and other solid tumours	I	CP and everolimus	≥10%
10	Goto *et al.*, 2011 [33]	19	12/7	57 (21–74)	Advanced NSCLC	I	CP,CB and PAC	All
11	Malempati *et al.*, 2011 [34]	47	24/23	15 (4–28)	Paediatric patients with refractory solid tumours and Ewing sarcoma	I/II	CIX	≥Grade 2
12	Pappo *et al.*, 2011 [4]	115	75/40	25 (8–78)	Recurrent or refractory Ewing sarcoma	II	R1507	≥5%
13	Ramalingam *et al.*, 2011 [11]	114	77/37	62.5	Advanced NSCLC	II	Erlotinib with placebo or R1507	All
14	Reidy *et al.*, 2010 [10]	64	33/31	61 (40–84)	Refractory metastatic colorectal cancer	II	CIX, with or without cetuximab	≥Grade 2
15	Lacy *et al.*, 2008 [35]	47	30/17	61.3 (42–81)	Multiple myeloma	I	CP	≥4%
Total:		772	476/296	50 (4–84)		I/II		

*QW:once a week, Q3W:once every three weeks. CIX, cixutumumab; CP, figitumumab; DOC, docetaxel; NSCLC, non-small cell lung cancer; PAC, paclitaxel; CB, carboplatin; Torisel, temsirolimus.

Data analysis

The overall average incidence of every enrolled AE, every grade ≥3 AE with an incidence higher than 0.1%, every dose-limited toxicity (DLT) and death which occurred in the enrolled studies was summarized or calculated. From the AE profile we extracted from all the enrolled studies, we selected AEs with an overall incidence of higher than 1.5% and analyzed them in our review (in total 31 types of AEs).

We individually performed the (continuity adjusted) chi-square test to compare the AE profile differences between three drugs and the whole patient population. In three specific enrolled studies, mAbs were used in a lower age group compared with the other studies. We therefore analyzed the AE incidence differences between the two age groups, also using the (continuity-adjusted) chi-square test. Furthermore, toxicities with combined therapies were compared with those in single mAb therapies. Finally, we discussed the AE characteristics of every mAb.

Results

Clinical material

Fifteen studies satisfied our inclusion criteria and entered our analysis. Every enrolled study was given a study number from 1 to 15. Five different mAbs were included in these studies. The total number of patients treated with different mAbs was 772. The baseline for reported AEs was shown in Table 1.

Merging of synonymous or similar AEs

We noted that some AEs depicted in different words were indeed synonymous and we adopted one of these words in our review. In addition, some terms contained the meaning of some other words, so we selected and used the terms that have a more extensive meaning. Furthermore, some AEs were similar and sometimes they were reported together, but sometimes they were reported separately, depending on the different studies concerning them. We put these AEs together in such circumstance. Table 2 shows all terms that met the three situations discussed above.

Overall overview of major toxicities

There were six single agent trials and nine combined-agent trials, of which two trials were case control studies. Toxicities reported by more than 10 of the enrolled studies were hyperglycaemia (15), nausea and vomiting (14), fatigue (13), anorexia (13) and skin reaction (11). Toxicities reported in more than 10.0% of the total patients were fatigue (28.8%), skin reaction (20%), diarrhoea (18.1%), nausea/vomiting (17.6%), hyperglycaemia (14.9%), anorexia (12.5%), muco/stomatitis (12.3%) and thrombocytopenia (10.6%) (Table 3). Grade ≥3 toxicities reported in no less than 2.5% of the patients were (Table 4) fatigue (4.9%), thrombocytopenia (3.6%), neutropenia (2.9%), hyperglycaemia (2.6%) and pain (2.5%). Despite the fact that the definitions of DLTs were not quite accordant in our enrolled studies, all the reported DLTs were summed up and are shown in Table 5. The top three frequently observed DLTs were thrombocytopenia (5), fatigue (4) and acneiform rash (3). Nine deaths were mAb-related in our analysis.

Table 2

Merging of synonymous or similar AEs

Terms used in this systematic review	Terms found in adverse effects reporting tables of enrolled studies
Anaemia	Haemoglobin, anaemia
Albumin decreased	Hypoalbuminaemia, albumin decreased
Arthralgia	Joint pain, arthralgia
Decreased appetite	Anorexia, decreased appetite
Dizziness	Ocular flashes of light, dizziness
Dyspepsia	Dyspepsia, eructation
Elevated AST/ALT	AST-SGOT ALT-SGOT, AST, ALT, elevated AST/ALT
Fatigue	Asthenia, fatigue
Flushing	Hot flashes/flushes, flushing
Hyperuracaemia	Raised uric acid concentration, hyperuracaemia
Hypomagnesaemia	Potassium decreased, hypomagnesaemia
Infection	Opportunistic infection, infection
Leukopenia	Leukocytes, leukopenia
Lymphopenia	Lymphocyte count decrease, lymphopenia
Muco/stomatitis	Mucositis, stomatitis, mucosal inflammation
Musculoskeletal pain	Extremity limb pain, skeletal pain, joint pain, muscle pain
Nail changes	Onychoclasis, nail changes
Nausea and vomiting	Nausea, vomiting
Neuropathy	Neuropathy, peripheral sensory neuropathy
Neutropenia	Neutrophils, neutropenia
Pain	Chest, back, abdominal or not defined pain, pain
Pyrexia	Pyrexia, fever
Skin reaction	Rash, dermatitis, pruritis, erythematous, skin reaction
Taste alteration	Taste disturbance, taste alteration
Thrombocytopenia	Thrombocytopenia, platelets
Hyperglycaemia	Blood glucose elevation, type 2 diabetes mellitus, hyperglycaemia
Weight decreased	Weight loss, weight decreased

The differences of AE incidence in the two age groups

In three of our enrolled studies, mAbs were used in some prepubertal teenage patients (the tumour types were mainly sarcoma). We compared the average AE incidence differences between the lower age group which was composed of the above three studies and the higher age group which included the rest of the 12 studies, using the (continuity-adjusted) chi-square test. Results were shown in Table 6. Of the total 31 types of AEs, 12 AE incidences were significantly ($P < 0.05$) higher in the lower age group, while six AE incidences were significantly ($P < 0.05$) lower in the same group. The AE profile was obviously better in the higher age group, indicating that anti–IGF-1R mAbs

Table 3

Overall AE profile of all enrolled clinical studies

AEs	Statistics from individual study (incidence, %)															TOTAL		
	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	AEs	Reporting studies	Incidence (%)
Fatigue	8.6	41.5	33.3	6.5	40.0	10.3		72.2	85.7		10.6	37.4	67.5	4.7	12.8	223	13	28.9
Skin reaction	5.7	24.5	40.5			13.7	1.3	55.6	52.4		2.1	7.0	72.8		4.3	152	11	19.7
Diarrhoea	2.9	7.5			40.0	6.9		50.0	28.6	47.4	2.1	20.9	59.6	1.6	8.5	142	12	18.4
Nausea and vomiting	2.9	17.0	26.2	6.5		6.9	1.3	27.8	66.6	26.3	6.4	31.3	31.6	6.3	8.5	134	14	17.4
Hyperglycaemia	2.9	9.4	71.4	4.3	4.8	17.2	18.8	16.7	61.9	5.3	10.6	19.1	5.3	4.7	6.4	116	15	15.0
Decreased appetite	5.7	13.2	33.3			6.9	1.3	27.8	42.9	73.7	6.4	20.9	11.4	1.6		95	12	12.3
Muco/stomatitis		5.7	45.2				1.3	44.4	100		2.1		35.1			93	7	12.0
Thrombocytopenia	8.6	24.5	47.6		2.4				52.4	84.2	8.5	10.4		1.6	8.5	85	10	11.0
Anaemia	2.9	11.3				6.9			52.4	68.4	21.3	15.7	6.1	1.6	14.9	76	10	9.8
Pain	2.9					6.9	1.3				2.1	48.7	6.1			68	6	8.8
Elevated AST/ALT	8.6		16.7	10.9		6.9			61.9		17.0	12.2			14.9	59	8	7.6
Musculoskeletal pain	2.9	15.1			9.5	6.9	2.5		52.4			25.2		1.6		58	8	7.5
Hypertriglyceridaemia			71.4						52.4		2.1%					42	3	5.4
Neutropenia			21.4						28.6	94.7	8.5	6.1				40	5	5.2
Constipation								11.1				18.3	13.2	3.1		40	4	5.2
Headache	2.9					10.3			19.0		2.1	22.6		4.7		38	6	4.9
Cough												13.0	15.8			33	2	4.3
Pyrexia		15.1					1.3				2.1	18.3		1.6		31	4	4.0
Hypercholesterolaemia			59.5						19.0							29	2	3.8
Dyspnoea												15.7	7.9			27	2	3.5
Leukopenia									28.6	94.7	4.3					26	3	3.4
Weight decreased	2.9					6.9			23.8		6.4	11.3				24	5	3.1
Muscle spasm				6.5		6.9		11.1					13.2		4.3	24	5	3.1
Dehydration	2.9							11.1			4.3		10.5			17	4	2.2
Creatinine elevation			16.7									6.1			4.3	16	3	2.1
Neuropathy										84.2						16	1	2.1
Hypophosphataemia	2.9								14.3		4.3	7.0				14	4	1.8
Elevated ALK phosphatase	2.9										2.1	9.6				14	3	1.8
Muscular weakness	2.9						7.5					5.2				13	3	1.7
Dyspepsia	2.9												9.6			12	2	1.6
Paronychia													10.5			12	1	1.6

*Study number.

might cause more serious side effects in prepubertal teenage patients. Such side effects included musculoskeletal pain, headache and pyrexia.

Toxicities of mAbs used as a single agent or combined with chemotherapy (inhibitors of epidermal growth factor receptor (EGFR)) and cytotoxic chemotherapy)

For figitumumab, it was used as a single agent in two enrolled studies, while it was used combined with carboplatin & paclitaxel in other two studies. We analyzed the differences in the AE profile in the two groups. Results showed that most of the AEs in the single-agent group had significantly lower incidences than in the combined-agent group (13 of 19 AEs, $P < 0.05$) (Table 7). Surprisingly, the incidence of elevated AST/ALT was higher in the single-agent group. Furthermore, it was reported that most patients treated with figitumumab in single agent studies did not develop severe hyperglycaemia [7, 8]. In our review, as was shown in Table 4, there were in total three patients (2.34%) who experienced grade ≥3 hyperglycaemia in the combined-agent group, while only one patient (1.32%) experienced grade ≥3 hyperglycaemia in the single-agent group (difference not significant, $P = 0.99$).

In study 8, the combination of erlotinib and cixutumumab had a relatively high level of EGFR-related side effects including acneiform rash and diarrhoea. The combined-agent patient group also showed a significant association with grades 3 and 4 fatigue [9]. Neither the randomized trial of cixutumumab in combination with the EGFR mAb cetuximab (Imclone) nor the randomized trial of R1507 with erlotinib reported any significantly higher increased incidence of rash or fatigue [10, 11].

Analysis on each drug

There were five anti-IGF-1R monoclonal antibodies enrolled in our review, namely R1507, cixutumumab (IMC-A12), figitumumab (CP-751 871), dalotuzumab (MK-0646) and ganitumab (AMG-479).

Table 4

All the grade ≥3 AEs (counted in numbers)

	Statistics from individual study (number of patients who experienced this AE)																TOTAL	
AEs	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Reporting Studies	Number	Incidence
Number of patients	35	53	42	46	42	29	80	18	21	19	47	115	114	64	47		772	
Fatigue		1	2	1	1			4	2			6	19	1	1	10	38	4.9
Thrombocytopenia		8	3		1					4	2	8		1		7	27	3.5
Neutropenia			4							16	2					3	22	2.8
Hyperglycaemia		4	2	1	1		1		1			3	6	1	1	10	21	2.7
Anaemia										2	4	9	2	1	1	6	19	2.5
Pain						1	1					17				3	19	2.5
Nausea and vomiting			1			1			3	1		1	8			6	15	1.9
Diarrhoea		1			1				1	1		2	7			6	13	1.7
Elevated AST/ALT	3		2			2					2	3			1	6	13	1.7
Decreased appetite			1							2		1	7	1		5	12	1.6
Skin reaction								3					8			2	11	1.4
Dyspnoea												2	6			2	8	1.0
Deep venous thrombosis						1							5			2	6	0.8
Hypophosphataemia									2		1	1				3	4	0.5
Muco/tomatitis			2										2			2	4	0.5
Constipation												4				1	4	0.5
Potassium decreased												4				1	4	0.5
Leukocytes										4						1	4	0.5
Dehydration											1		2			2	3	0.4
Hyperuricaemia						1				2						2	3	0.4
Elevated ALK phosphatase	1											2				2	3	0.4
Hyponatraemia										3						1	3	0.4
Musculoskeletal pain		1										1				2	2	0.3
Elevated γGT					1	1										2	2	0.3
Cough												2				1	2	0.3
Dyspepsia													2			1	2	0.3
Bilirubin elevation												2				1	2	0.3

*Study number.

Table 5

Number of DLTs

	Statistics from individual study (DLT number)						
AEs	2† (Ganitumab)‡	3 (CIX and Torisel)	7 (dalotuzumab)	8 (Erlotinib and CIX)	10 (CP and CB and PAC)	11 (CIX)	Tatal number
Thrombocytopenia	2	1			1	1	5
Fatigue				4			4
Acneiform rash				3			3
Febrile neutropenia		1					1
Leukocytoclastic vasculitis			1				1
Hyperuricaemia					*1		1
Hypermagnesaemia					*1		1
Hyponatraemia					*1		1
Hyperkalaemia					*1		1
Dehydration						1	1

*DLT observed in the same patient; †study number; ‡drugs. CB, carboplatin; CIX, cixutumumab; CP, figitumumab; DLT, dose-limited toxicities; PAC, paclitaxel; Torisel, temsirolimus.

R1507 There were three studies in our analysis concerning this drug. This mAb seemed to show a worse AE profile than cixutumumab and figitumumab. The top three frequently observed AEs for this drug were fatigue (46.6%), diarrhoea (35.2%) and skin reaction (35.2%). Compared with the whole patient population, patients who used this drug reported 16 kinds of AEs that showed significantly ($P < 0.05$) higher incidence. (Table 8). Most of them also showed significantly ($P < 0.05$) higher incidences than for the figitumumab and cixutumumab groups

Table 6

The differences in AE-incidences in the two age groups

Median (range) age (years)	Lower age group incidence 23 (4–78)	Number of AEs	Higher age group incidences 58 (18–84)	Number of AEs	X^2	P
Hyperglycaemia	16.8	32	14.5	84	0.5935	0.4411
Nausea and vomiting	21.5	41	16.0	93	2.9864	0.0840
Fatigue	26.7	51	29.6	172	0.5895	0.4426
Anorexia	15.2	29	11.4	66	1.9473	0.1629
Diarrhoea	14.1	27	19.8	115	3.0649	0.0800
Skin reaction	6.8	13	23.9	139	26.6377	0.0000
Anaemia	15.7	30	7.9	46	9.8269	0.0017
Thrombocytopenia	8.4	16	11.9	69	1.7963	0.1802
Musculoskeletal pain	16.2	31	4.6	27	27.7561	0.0000
Elevated AST/ALT	12.6	24	6.0	35	8.7140	0.0032
Pain	30.9	59	1.5	9	154.0618	0.0000
Muco/stomatitis	0.5	1	15.8	92	31.8048	0.0000
Headache	15.7	30	1.4	8	63.0713	0.0000
Weight decreased	9.4	18	1.0	6	33.6032	0.0000
Neutropenia	5.8	11	5.0	29	0.1725	0.6779
Muscle spasm	1.0	2	3.8	22	3.5813	0.0584
Dehydration	1.0	2	2.6	15	0.9401	0.3322
Pyrexia	11.5	22	1.5	9	37.0658	0.0000
Constipation	11.0	21	3.3	19	17.4583	0.0000
Hypophosphataemia	5.2	10	0.7	4	14.2358	0.0002
Muscular weakness	3.1	6	1.2	7	2.1914	0.1388
Dyspnoea	9.4	18	1.5	9	26.4126	0.0000
Hypertriglyceridaemia	0.5	1	7.1	41	11.9265	0.0006
Elevated ALK phoshatase	6.3	12	0.3	2	25.2321	0.0000
Leukopenia	1.0	2	4.1	24	4.2001	0.0404
Creatinine elevation	3.7	7	1.5	9	2.2139	0.1368
Hypercholesterolaemia	0.0	0	5.0	29	9.9057	0.0016
Cough	7.9	15	3.1	18	7.9437	0.0048
Dyspepsia	0.0	0	2.1	12	2.7711	0.0960
Neuropathy	0.0	0	2.8	16	4.1000	0.0429
Paronychia	0.0	0	2.1	12	2.7711	0.0960

(including all patients using figitumumab or cixutumumab), except muco/stomatitis dehydration and muscle spasm. Meanwhile, the incidence of hyperglycaemia, thrombocytopenia, neutropenia, hypertriglyceridaemia, leukocytes, hypercholesterolaemia and neuropathy were all significantly ($P < 0.05$) lower than the overall incidence in the whole population (thrombocytopenia, neutropenia and hypertriglyceridaemia were also significantly lower than in the figitumumab and cixutumumab groups). Other AEs which showed no significant differences are also shown in Table 8.

Cixutumumab There were four studies in our analysis concerning this drug. Its AEs profile seemed to be better than R1507 and figitumumab as shown in Table 8. The top three frequently observed AEs for this drug were hyperglycaemia (24.0%), fatigue (20.5%) and hypertriglyceridaemia (18.6%). Comparing with the overall incidence of the whole population, six kinds of AEs showed significantly ($P < 0.05$) higher incidences (Table 8). These AEs were mainly laboratory abnormalities (hyperglycaemia, hypertriglyceridaemia, hypercholesterolaemia, elevated AST/ALT, muco/stomatitis and thrombocytopenia), most of which also showed a significantly ($P < 0.05$) higher incidences than the figitumumab and R1507 groups, except for thrombocytopenia, elevated AST/ALT and muco/stomatitis. Seven kinds of AEs showed significantly ($P < 0.05$) lower incidences than the whole population, including musculoskeletal pain, which also maintained a lower incidence than in the figitumumab and R1507 groups.

Dalotuzumab There was only one study concerning this drug in our analysis. From the single study; we observed that every AE incidence was below 2.5% except hyperglycaemia (18.8%) but there was inadequate evidence to affirm that this drug had a better AE profile than the other drugs.

Figitumumab The highest number of studies in our review was concerning this drug (six studies). This is the only fully

Table 7

Comparation of AE-incidences between combination groups and single agent groups of figitumumab

AEs with a higher incidence in the combination group	A* (in total 61 patients)	%	B (in total 76 patients)	%	X^2	*P*
Decreased appetite	14	0.23	2	0.03	13.5448	0.0002
Diarrhoea	22	0.36	6	0.08	16.5150	0.0000
Thrombocytopenia	17	0.28	4	0.05	13.3236	0.0003
Neutropenia	18	0.30	0	0.00	25.8184	0.0000
Leukocytes	18	0.30	0	0.00	25.8184	0.0000
Neuropathy	16	0.26	0	0.00	22.5704	0.0000
AEs with a higher incidence in the single-agent group						
Elevated AST/ALT	0	0.00	9	0.12	5.9226	0.0149
AEs with a similar incidence in the two groups						
Hyperglycaemia	3	0.05	8	0.11	0.7819	0.3766
Nausea and vomiting	5	0.08	6	0.08	0.0633	0.8013
Fatigue	13	0.21	9	0.12	2.2511	0.1335
Skin reaction	0	0.00	6	0.08	3.3276	0.0681
Anaemia	13	0.21	9	0.12	2.2511	0.1335
Musculoskeletal pain	4	0.07	2	0.03	0.4843	0.4865
Pain	0	0.00	2	0.03	0.3133	0.5757
Headache	0	0.00	3	0.04	0.9637	0.3262
Weight decreased	0	0.00	2	0.03	1.6290	0.2018
Muscle spasm	0	0.00	4	0.05	3.3071	0.0690
Creatinine elevation	0	0.00	2	0.03	0.3133	0.5757

*A, number of AEs in combination group; B, number of AEs in single agent group.

human IgG2 antibody (the others have a IgG1 backbone) in our review and has the longest $t_{1/2}$ of approximately 20 days [12]. The top three frequently observed AEs for this drug were fatigue (21.1%), diarrhoea (16.7%) and anaemia (16.2%). Six kinds of AEs showed significantly ($P < 0.05$) higher incidences than the whole population, most of which also showed significantly ($P < 0.05$) higher incidences than the R1507 and cixutumumab groups (Table 6), except thrombocytopenia and neutropenia. Eight kinds of AEs showed significantly ($P < 0.05$) lower incidences than in the whole population, including skin reaction, which also showed a significantly ($P < 0.05$) lower incidence than in the R1507 and cixutumumab groups.

Ganitumab There was also only one study concerning this drug in our analysis. In the single study, the top three frequently observed AEs for this drug were fatigue (41.5%), thrombocytopenia (24.5%) and skin reaction (24.5%).

Discussion

The identification of specific AEs related to anti-IGF-1R mAbs

Of all the AEs reported in clinical studies, many were often related to the IGF-1R mAbs. Still it was significant to identify specific AEs related to anti-IGF-1R mAbs. To overcome this problem, in this review we tried to focus our attention on a limited number of AEs with high frequencies and may relate to the mechanism of action of the mAbs. Four important AEs that may relate to mAbs were discussed in the following context. From the whole AEs profile we extracted from all the enrolled studies, we selected AEs with an overall incidence of higher than 1.5% and discussed them in our review (in total 31 kinds of AEs).

The characteristics of some important AEs related to anti-IGF-1R mAbs and possible mechanism/explanation of hyperglycaemia and hypoglycaemia

Hyperglycaemia and hypoglycaemia The highest incidence of hyperglycaemia was reported in study 3 (cixutumumab and temsirolimus) as 71.4%. Patients with previous glucose intolerance or treated with concomitant steroids were more susceptible to developing hyperglycaemia [12]. The overall incidence of hyperglycaemia in our analysis was 14.4%, frequently observed but lower than the data reported by two former reviews (25% [13], 20% [12]). It was reported in a single study that approximately 50% of patients showed abnormal glucose tolerance throughout that trial [14], so hyperglycaemia was an obviously common and mechanism-based toxicity. On the other hand, it appears usually to be easily controllable with metformin and other anti-diabetic agents. Interestingly, in a former review [12], it was reported that the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) was not suited for evaluating toxicities of targeted drugs, because it considered a serum glucose

Table 8

Comparison of AE-incidences between specific mAbs and the whole patient population

	Incidence for specific mAb	Number of AEs	Incidence in whole population	Total number of AEs	X^2	*P*
AEs with lower incidences in mAb groups						
R1507						
Hyperglycaemia	11.0	29	15.0	116	16.9961	0.0000
Thrombocytopenia	5.7	15	11.0	85	13.4768	0.0002
Neutropenia	2.7	7	5.2	40	4.4013	0.0359
Hypertriglyceridaemia	0.0	0	5.4	42	16.1373	0.0001
Leukocytes	0.0	0	3.4	26	9.1201	0.0025
Hypercholesterolaemia	0.0	0	3.8	29	10.7523	0.0010
Neuropathy	0.0	0	2.1	16	4.4628	0.0346
Cixutumumab						
Fatigue	20.5	35	28.9	223	4.9917	0.0255
Diarrhoea	6.4	11	18.4	142	14.7348	0.0001
Musculoskeletal pain	0.6	1	7.5	58	11.4566	0.0007
Pain	0.6	1	8.8	68	13.9597	0.0002
Constipation	2.3	4	5.2	40	4.2062	0.0403
Pyrexia	1.2	2	4.0	31	4.3009	0.0381
Cough	0.0	0	4.3	33	8.5063	0.0035
Figitumumab						
Hyperglycaemia	12.7	26	15.0	116	16.2414	0.0001
Fatigue	21.1	43	28.9	223	4.9612	0.0259
Skin reaction	8.3	17	19.7	152	14.5335	0.0001
Pain	1.0	2	8.8	68	14.8512	0.0001
Muco/stomatitis	10.3	21	12.0	93	10.2296	0.0014
Constipation	0.0	0	5.2	40	12.2793	0.0005
Pyrexia	0.0	0	4.0	31	9.2086	0.0024
Cough	0.0	0	4.3	33	9.8750	0.0017
AEs with higher incidences in mAb groups						
R1507						
Nausea and vomiting	27.7	73	17.4	134	13.0384	0.0003
Fatigue	46.6	123	28.9	223	27.7232	0.0000
Diarrhoea	35.2	93	18.4	142	31.7855	0.0000
Skin reaction	35.2	93	19.7	152	26.3049	0.0000
Pain	24.2	64	8.8	68	42.1505	0.0000
Muco/stomatitis	15.2	40	12.0	93	10.7145	0.0011
Headache	10.2	27	4.9	38	10.5165	0.0012
Constipation	13.6	36	5.2	40	21.4960	0.0000
Muscle spasm	5.7	15	3.1	24	4.0809	0.0434
Pyrexia	8.0	21	4.0	31	7.1672	0.0074
Dyspnoea	10.2	27	3.5	27	18.0338	0.0000
Cough	12.5	33	4.3	33	22.6890	0.0000
Dyspepsia	4.5	12	0.6	5	16.1279	0.0001
Elevated ALK phosphatase	4.5	12	1.8	14	6.1119	0.0134
Dehydration	4.9	13	2.2	17	5.3829	0.0203
Paronychia	4.5	12	1.6	12	7.8280	0.0051
Cixutumumab						
Hyperglycaemia	24.0	41	15.0	116	23.3586	0.0000
Thrombocytopenia	14.6	25	11.0	85	10.0313	0.0015
Elevated AST/ALT	8.8	15	7.6	59	4.1693	0.0412
Muco/stomatitis	16.4	28	12.0	93	12.2882	0.0005
Hypertriglyceridaemia	18.1	31	5.4	42	32.1086	0.0000
Hypercholesterolaemia	14.6	25	3.8	29	30.5818	0.0000
Figitumumab						
Anaemia	16.2	33	9.8	76	6.5211	0.0107
Thrombocytopenia	15.7	32	11.0	85	11.1615	0.0008
Elevated AST/ALT	13.2	27	7.6	59	9.6979	0.0018
Neutropenia	11.8	24	5.2	40	12.6551	0.0004
Leukocytes	11.8	24	3.4	26	23.4071	0.0000
Neuropathy	7.8	16	2.1	16	16.9329	0.0000

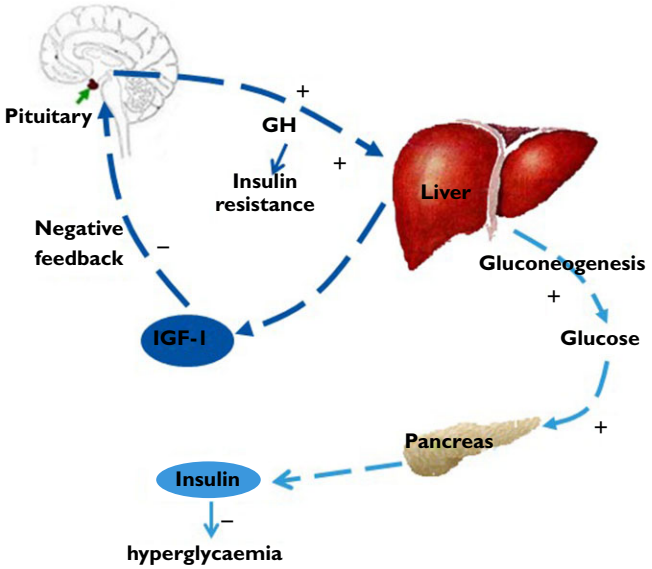

Figure 1

Mechanisms of hyperglycaemia. IGF-IR mAbs also act on normal tissues besides tumour cells. They block IGF-IRs that control the homeostasis of the GH-IGF-I axis as well. This reduces the feedback inhibition of GH secretion, which in turn leads to elevation in GH. Elevation in GH can lead to insulin resistance in classic insulin target organs, and increased gluconeogenesis and subsequent elevation in glucose. Glucose elevation in turn cause increased insulin secretion, which commonly corrects hyperglycaemia. Furthermore, the elevated GH concentrations stimulate increased IGF-I production by the liver, leading to IGF-I elevation in the circulation. IGF-IR, insulin-like growth factor type I receptor; GH, growth hormone; IR, insulin receptor

concentration above 250 mg dl^{-1} as grade 3, which might result in defining it as a dose-limiting toxicity while being clinically insignificant. The authors declared that the NCI-CTCAE should be reviewed or specific guidelines for the management of tolerable, mechanism-based toxicities should be developed.

The mechanism of hyperglycaemia is still unclear. There was a theory indicating that the cross reactivity of the anti-IGF-1R mAbs with the insulin receptor (IR) leads to hyperglycaemia, but it is not convincing enough because there is strong evidence to show that these mAbs can all act to spare the IR. Furthermore, although some antibodies do target, IR/IGF-1R hybrids', these hybrid receptors do not play a predominant role in the regulation of glycaemia, and they are more sensitive to IGFs than to insulin [15–17]. More complicated mechanisms (shown in Figure 1) to explain hyperglycaemia are as follows: besides tumour cells, IGF-IR monoclonal antibodies also act on normal tissues. Most of all, IGF-IRs in the hypothalamic-pituitary axis that is involved in homeostatic feedback control are also targeted. This reduces the feedback inhibition of growth hormone secretion, thus lead to elevation in growth hormone (GH). Elevation in GH can cause insulin resistance in classic insulin target organs, increased gluconeogenesis, and thus leading to elevations in glucose concentrations. This in turn results in increased insulin secretion which commonly corrects hyperglycemia to some extent. Furthermore, the elevated GH concentrations stimulate increased IGF-I production by the liver, accounting for the observed IGF-I elevations in the circulation [15, 18].

Finally, besides hyperglycaemia, hypoglycaemia was also observed in another clinical trial, although it was not severe and no treatment was required [19]. We speculated that hypoglycaemia might be caused by elevated IGF-I concentrations in the circulation, since it was reported that IGF-I could reduce hepatic glucose production and increases peripheral glucose uptake [20, 21]. Moreover, the inverse effect of elevated GH mentioned above is not sufficient to reverse the effect of IGF-1 elevation.

Thrombocytopenia In study 9 (Figitumumab & Everolimus), thrombocytopenia was mentioned as the most commonly observed reason for treatment delay. In the present review, thrombocytopenia was rare when figitumumab was given as single agent (0% and 8.5%), as similarly described in study 5 [22]. This is important because haematological toxicity has been shown to be dose limiting for anti-IGF-1R antibodies with an IgG1 backbone [23]. Figitumumab is a fully human IgG2 antibody and, consequently, is expected to be a poor stimulator of antibody mediated cytotoxicity and complement fixation [24], so the haematological toxicities related to this drug were supposed to be lower than the other IgG1 backbone mAbs. In our review, the overall incidence of thrombocytopenia in patients who received figitumumab was 15.7%, higher than patients who received R1507 (5.7%, $P = 0.00$), cixutumumab (14.6%, $P = 0.77$), dalotuzumab (single study, 0%) and the whole patient population (11.0%, $P = 0.07$). Only the incidence for ganitumab (single study, 24.5%, $P = 0.13$) was higher, but possibly this result might also indicate that obviously more haematological toxicities arose when figitumumab is combined with chemotherapies.

Neutropenia It was reported in study 6 (figitumumab) that there was no apparent effect of figitumumab on the frequency or severity of observed neutropenia, as with other mAbs like dalotuzumab and ganitumab. The authors concluded that neutropenia did not seem to be significantly worsened when combined with chemotherapy [25, 26]. However, in our analysis, when figitumumab was combined with carboplatin and paclitaxel, the incidence of neutropenia was significantly higher than in the single figitumumab group (29.5% *vs.* 0%, $P = 0.00$) as is shown in Table 7. Besides, the suspended study of a phase III trial of carboplatin and paclitaxel with or without figitumumab also revealed that there were more life-threatening AEs in patients who received figitumumab combined with

chemotherapy. So whether and how figitumumab should be combined with chemotherapy is somehow worth discussing. More information about inherent side effects of combined chemotherapies, clinical efficiency of mAbs and biomarkers should be included in this discussion, too.

Cardiotoxicity Interestingly, despite of the expression of IGF-1R in vascular smooth muscle and endothelial cells, and potential cardiotoxicity associated with anti-IGF-1R mAbs, no cardiac toxicities were reported in any of the enrolled studies. Even in the case of sarcoma patients treated with figitumumab in study 6, three quarters of the patients were pretreated with anthracyclines but none developed cardiotoxicity [27]. However, cardiotoxicities were reported to be more frequent when figitumumab was in combination with carboplatin and paclitaxel compared with carboplatin and paclitaxel in patients with non-small cell lung cancer (NSCLC) [1, 28], although the trial was suspended as mentioned above.

Conclusion

Differences in AE incidences exist between individual anti-IGF-1R mAbs, as well as between the two age groups studied, and combination with chemotherapies seem to cause more AEs. These data suggest that when using this class of drugs, some more frequently observed AEs for specific mAbs should be paid adequate attention, and it is essential to choose the proper drug and combination with chemotherapies to reduce the occurrence of AEs. Furthermore, prepubertal patients who receive these mAbs possibly need more prudent medical care.

The potential insufficiencies of this systematic review

The number of the enrolled studies was not quite sufficient and we only searched one database, namely Pubmed for our analysis. In some enrolled studies, specific mAbs were combined with chemotherapies, and some of these studies selected the mAb-related toxicities while the others did not. Some toxicities not related to mAbs might thus be extracted from the latter studies.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and we declare this work was supported by Natural Science Foundation of China (81141100), Provincial Science and Technology Development Planning of Shandong (2011GGH21819) and the Natural Science Foundation of Shandong Province of China (ZR2011HM077). There are no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and there are also no other relationships or activities that could appear to have influenced the submitted work.

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